

ORIGINAL ARTICLE

The onset of allergic rhinitis in Japanese atopic children: A preliminary prospective study

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Abstract

Conclusion: This preliminary prospective study suggests that background factors may differ among allergic diseases. The beneficial interventions for reducing development of allergic rhinitis (AR) are also effective for the prevention of subsequent onset of bronchial asthma (BA). **Objective:** To determine the risk factors associated with onset of AR in atopic children in a prospective study. **Methods:** All patients with atopic dermatitis (AD) or food allergy with or without BA who visited the Pediatric Unit of Chiba University Hospital from 2005 to 2006 were enrolled in the study and received allergy examinations every 3–6 months. **Results:** A total of 100 patients were followed up for more than 2 years. Among the 60 patients without BA at entry to the study, 12 developed BA during the follow-up period. Development of AR preceded BA in 10 of the 12 patients (83.3%). In the background factors at the entry, positive sensitization to house dust mite (HDM) was significantly related to development of BA. Among the 48 patients without AR, 20 developed AR. High titers of serum HDM-specific IgE and high eosinophil counts in blood, and detection of eosinophils in nasal smears at the entry were significantly related to development of AR.

Keywords: Bronchial asthma, atopic dermatitis, food allergy, house dust mite specific IgE

Introduction

The concept of chronological development of food allergy (FA), atopic dermatitis (AD), bronchial asthma (BA), and allergic rhinitis (AR) in children with atopic risk factors is referred to as ‘allergic march.’ However, the detailed interactions and relationships among these allergic diseases have yet to be clarified. Settupane et al. [1] found that college students with AR developed BA at a rate three times higher than those without AR in a 23-year follow-up study. Similar studies in Finland [2] and the United States [3] also concluded that AR was an independent risk factor for development of BA. However, the asthma type (atopic or non-atopic) and development of AR in the follow-up period were

not examined in these retrospective studies. Furthermore, the underlying mechanisms of development of allergic diseases are unclear and might differ with age, gender, and ethnicity.

Early intervention is currently thought to be important for prevention of progression of allergic diseases to more serious conditions. Therefore, an understanding of the interactions among allergic diseases in the development phase is required for establishment of an optimal strategy for early intervention, and particularly for secondary intervention. In this study, we prospectively examined the risk factors associated with onset of AR in atopic children who were closely followed at our institute for more than 2 years (mean 3.5 years), although the number of examined subjects was limited. Onset of AR preceded development of

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BA in many patients, and high serum titers of house dust mite (HDM)-specific IgE and increased eosinophil counts in blood and nasal smears were identified as possible predictive factors for development of AR.

Material and methods

Subjects

All AD or FA patients with or without asthma who visited the Pediatric Unit of Chiba University Hospital from 2005 to 2006 were enrolled in the study. Prior approval for the study was obtained from the Ethics Committee of Chiba University. Written, witnessed, informed consent was obtained from the parents of all patients.

Study protocol

All patients were examined by the same otorhinolaryngologist (S.Y.) and pediatrician (N.S.), who specialize in allergology. The examination included a nasal inspection, a respiratory test including spirometry and peak flow monitoring, and allergy tests for total IgE, HDM, Japanese cedar pollen, orchard grass, egg, wheat-specific IgE, ratio of eosinophils in leukocytes in peripheral blood, and cytology of a nasal smear. The respiratory test was conducted to determine the extent and change in lower airway obstruction. Positive sensitization to inhalants and food allergens was a necessary condition for diagnosis of AR and FA, respectively. The allergy tests were performed every 3–6 months.

Diagnosis of allergic diseases

Diagnosis of AR was based on the following criteria: representative symptoms of AR (e.g. paroxysmal sneezing, runny nose, nasal congestion, nasal itching, and eye itching) that persisted for more than 2 weeks, positive sensitization to typical allergens, and positive identification of eosinophils in a nasal smear. Nasal cytology has been shown to be useful in diagnosis of AR in children [4]. Positive sensitization was defined as a serum CAP-radioallergosorbent test (CAP-RAST, SRL Inc., Tokyo, Japan) score ≥ 2 . The specific IgE level was ≥ 0.7 UA/ml.

Diagnosis of FA was based on symptoms after a meal (e.g. eczema, cough, vomiting, and diarrhea), positive sensitization to foods, and food challenge tests. Diagnosis of AD was based on symptoms of eczema with pruritus that repeatedly aggravated and palliated. A personal or parental history of allergic diseases and a high IgE titer were also considered in the AD diagnosis [5]. Diagnosis of BA was based on a

history of symptoms and reversible bronchoconstriction. Patients or their parents completed a daily diary of respiratory symptoms (e.g. recurrent wheeze, dyspnea, exercise-induced symptoms, and symptoms causing waking at night) and these were checked by a doctor.

Treatment of the diseases

Allergic diseases were treated using the Japanese practical guidelines [6]. Local application of steroid ointment and oral antihistamines were used for AD. FA was treated by removal of the causal foods from the diet. Inhalation of steroids or leukotriene receptor antagonists was used for control of BA, with inhalation of β -blockers when needed based on the severity of symptoms. Oral antihistamines were mainly used for AR. Nasal steroids were only used in a few patients because these drugs are not approved for patients under 6 years old in Japan.

Statistical analysis

Data analysis was performed with two-tailed tests at a significance level of 5%. A Mann-Whitney U test was used for comparison of age and background factors at the first examination and in the follow-up period. A chi-squared test was used for other factors. All analyses were performed using SAS v. 8.02 (Cary, NC, USA).

Results

Background of subjects

A total of 114 pediatric patients were enrolled in the study and 100 patients were followed for more than 2 years. Fourteen patients dropped out of the study for personal reasons. The mean follow-up period was 3.5 ± 1.9 years. The background of the 100 patients at entry, including diagnosis, age, gender, birth order (first child or not), breast feeding, parental history of allergic disease (AD, BA, and HDM AR), parental smoking, pets, ratio of eosinophils in leukocytes in peripheral blood, and HDM-specific IgE are shown in Table I.

Follow-up of 60 patients without BA at the first examination

Among the 60 patients who did not have BA at the time of entry, 12 developed BA in the follow-up period. A comparison of the background factors at the time of entry between these 12 patients and the 48 patients who did not develop BA is shown in Table II. The HDM sensitization rate was higher ($p < 0.05$) in

Table I. Backgrounds of the enrolled patients at the time of entry to the study ($n = 100$).

Parameter	%
Boys	76.0
First child	67.0
Breast feeding	76.0
Parental medical history of allergic diseases*	37.0
Parental smoking	28.0
Pet	14.0
Ratio of blood eosinophils	
<5%	51.0
≥5%	49.0
HDM-specific IgE (UA/ml)	
<0.70	24.0
0.70–17.5	20.0
>17.5	56.0
Diseases present	
BA only	9.0
BA + AR	27.0
BA + AD (± FA)	4.0
AD (± FA)	60.0

Age at time of entry was 4.0 ± 2.7 years (mean $\pm$ SD) and the follow-up period was 3.5 ± 1.9 years. AD, atopic dermatitis; BA, bronchial asthma; FA, food allergy; HDM, house dust mite.

*Parental history of allergic disease included at least one of three diseases (AD, BA, and HDM AR).

patients who developed BA. Age, gender, birth order, breast feeding, parental clinical history, parental smoking, pets, diagnosis of HDM AR, detection of nasal eosinophils, and ratio of blood eosinophils did not differ significantly between the groups. Titers of HDM-specific IgE were not correlated with development of BA. Of the 12 patients with newly developed BA, 5 had AR at the time of entry and 7 developed AR in follow-up (Figure 1). In five of these seven patients, onset of AR occurred more than 3 months earlier than onset of BA. In the other two patients, the onset times for AR and BA were within 3 months of each other. Therefore, development of AR preceded BA in 10 of 12 patients (83.3%) with new onset BA.

Follow-up of 48 patients without AR at the first examination

Among 48 patients who did not have AR at the time of entry, 20 developed AR in the follow-up period. A comparison of the background factors at entry between these 20 patients and the 28 patients who did not develop AR is shown in Table III. Patients with new onset AR had significantly higher levels of

eosinophils in nasal smears ($p < 0.01$), ratio of blood eosinophils ($p < 0.01$), and HDM-specific IgE ($p < 0.01$). HDM-specific IgE titers were correlated with development of AR. Age, gender, birth order, breast feeding, parental clinical history, parental smoking, pets, and diagnosis of BA did not differ significantly between the groups. Among the 48 patients initially without AR, eosinophils in the nasal smear were detected in 8 at the time of entry and in another 15 during follow-up. Of these 23 patients, 20 (86.4%) developed AR. Among the 20 patients with new onset AR, 14 (70.0%) were not complicated with BA (Figure 1). Of the six patients with AR and BA, four (20.0%) had BA at the time of entry and two (10.0%) developed BA at the same time as onset of AR.

Influence of treatment on development of new allergic diseases

The association of development of BA and AR with the severity of eczema during the follow-up period is shown in Table IV. The severity of eczema was significantly associated with development of AR ($p < 0.05$), but not with development of BA.

Discussion

Epidemiological studies have shown that BA and AR often co-exist, and the Allergic Rhinitis Impact on Asthma (ARIA) guidelines [7] recommend treating these conditions as a series of airway diseases, rather than as separate diseases. However, the interactions and relationships in the development of these allergic diseases have not been clarified. In the current prospective study, in which pediatric patients with AD or FA were followed up for a mean period of 3.5 years, we found that development of AR preceded that of BA in atopic children with AD or FA. This result is in agreement with several retrospective studies [1–3] and suggests that AR is an independent risk factor for development of BA.

In a recent birth cohort study of the sequential progression of multiple allergic diagnoses using the General Practice Research Database in the UK [8], diagnosis of eczema followed by asthma, which was in turn followed by rhinitis, was found to be the most common trajectory. However, as pointed out by the authors, rhinitis may have been under-diagnosed in the study. Diagnosis of AR has the risk of inclusion of a high rate of false-positive or false-negative cases because of the different concerns of patients, parents, and doctors. AR is sometimes difficult to distinguish from acute infectious rhinitis and even healthy people may exhibit mild, nonspecific nasal symptoms such as sneezing and nasal secretion. Thus, an allergic

Table II. Association between background factors and the development of bronchial asthma (BA).

Parameter	Patients without BA on entry to study (<i>n</i> = 60)		<i>p</i> value
	12 patients with newly developed BA	48 patients without BA	
Age at time of entry (years) (mean ± SD)	2.5 ± 0.7	3.3 ± 2.5	0.47
Follow-up period (years) (mean ± SD)	2.8 ± 1.9	3.6 ± 1.4	0.28
Background factors at time of entry (%)			
Boys	91.7	72.9	0.32
First child	83.3	64.6	0.21
Breast feeding	91.7	85.4	0.92
Parental medical history of allergic diseases*	58.3	37.5	0.33
Parental smoking	25.0	18.8	0.94
Pet	20.0	8.3	0.75
Diagnosis of HDM AR	41.7	41.7	0.74
Positive for eosinophils in nasal smear	50.0	52.1	0.85
Ratio of blood eosinophils in nasal smear			0.061
<5%	25.0	60.4	
≥5%	75.0	39.6	
HDM-specific IgE (UA/ml)			< 0.05
<0.70	0	33.3	
>0.70	100	66.7	

AD, atopic dermatitis; AR, allergic rhinitis; FA, food allergy; HDM, house dust mite.

*Parental history of allergic disease included at least one of three diseases (AD, BA, and HDM AR).

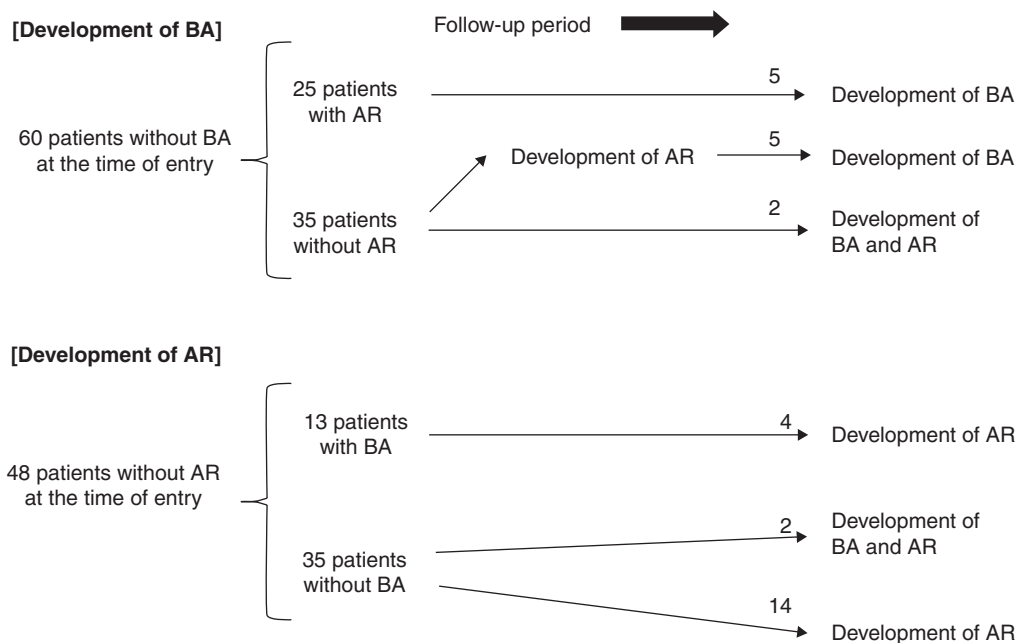


Figure 1. Development of allergic rhinitis (AR) preceded bronchial asthma (BA) in 10 (83.3%) of 12 patients with new onset BA. In contrast, development of BA preceded AR in only 4 (20.0%) of 20 patients with new onset AR.

Table III. Association between background factors and the development of allergic rhinitis (AR).

Parameter	Patients without AR on entry to study (<i>n</i> = 48)		<i>p</i> value
	20 patients with newly developed AR	28 patients without AR	
Age at time of entry (years) (mean ± SD)	2.9 ± 1.8	3.5 ± 3.2	0.66
Follow-up period (years) (mean ± SD)	4.1 ± 1.2	2.7 ± 2.0	0.10
Background factors at time of entry (%)			
Boys	80.0	82.1	0.85
First child	85.0	71.4	0.45
Breast feeding	75.0	92.9	0.19
Parental medical history of allergic diseases*	20.0	35.7	.23
Parental smoking	20.0	35.7	0.39
Pet	5.0	7.1	0.76
Diagnosis of BA	20.0	32.1	0.54
Positive for eosinophils in nasal smear	40.0	0	< 0.01
Ratio of blood eosinophils			< 0.01
<5%	40.0	85.7	
≥5%	60.0	14.3	
HDM-specific IgE (UA/ml)			< 0.01
<0.70	20.0	60.7	
0.7–17.5	20.0	25.0	
>17.5	60.0	14.3	

AD, atopic dermatitis; HDM, house dust mite.

*Parental history of allergic disease included at least one of three diseases (AD, BA, and HDM AR).

examination is necessary to avoid a high incidence of false positives and false negatives.

In the current study, detection of eosinophils in nasal smears, increased peripheral blood eosinophils, and high HDM-specific IgE in serum were identified as risk factors for onset of AR in atopic children with AD or FA. However, only 20% of the patients with new onset AR had preceding BA, while 70% of patients developed AR without BA.

Many factors are likely to be involved in development of BA and a subgroup of younger children may develop BA before AR. However, the mean ages at entry of patients without BA and with BA were 3.2 and 5.5 years, respectively, and rates of AR in these subjects were 41.6 and 67.5%, respectively. Thus, AR can develop at a younger age and we were unable to identify BA as an independent risk factor for AR.

Table IV. Association between the control of eczema and the development of bronchial asthma (BA) or allergic rhinitis (AR).

Patient group	Status	Control of eczema (%)			<i>p</i> value
		<i>n</i>	Good*	Poor†	
Subjects without BA at entry to study		60			0.75
	BA developed	12	50.0	50.0	
	BA undeveloped	48	50.0	50.0	
Subjects without AR at entry to study		39			< 0.05
	AR developed	18	38.8	61.1	
	AR undeveloped	21	76.2	23.8	

*Control of eczema was defined as 'Good' when the skin was dry and eczema was not observed clearly.

†Control of eczema was defined as 'Poor' when eczema was observed clearly.

In recent years, many countries have experienced an increase in the prevalence of AR. Natural resolution of AR is not commonly observed, particularly in childhood, and most pediatric patients with AR grow to adulthood without natural improvement. Genetic and environmental factors appear to be involved in onset of AR, as seen with many other diseases [9–12]. The relevance of genetic factors cannot be ignored, but it appears that environmental factors have played a major role in the recent increase of AR. Factors that change the predisposition to produce IgE are thought to have contributed to this increase. The findings in the current study are consistent with this suggestion, since development of AR was associated with an increased titer of HDM-specific IgE, but was not clearly linked to parental history of allergy.

Early intervention strategies to inhibit the increase of specific IgE are important in the management of AR. Allergen avoidance is clearly important for prevention of AR, but may not achieve effective results [13]. Allergen-specific immunotherapy is the only current treatment with the potential for long-term cure of AR. Randomized controlled trials (RCTs) have shown that antigen-specific immunotherapy is also effective for changing the natural course of allergic diseases [14], decreasing antigen-specific IgE [15], and reducing new allergic sensitization [16]. However, administration by a subcutaneous route as an early intervention is difficult in children, in particular, because it is associated with a risk, albeit low, of anaphylactic shock and the inconvenience of frequent visits to a physician [17]. A recent review of RCTs of sublingual immunotherapy (SLIT) for AR suggested that this approach is safe and easy for children [18]. Thus, SLIT may be effective as an alternative route of administration and as an early intervention strategy.

Poor control of AD is associated with a risk of development of AR, since damage to the skin barrier by AD itself and by resultant scratching might aggravate skin sensitization to allergens [19]. A clinical RCT of the efficacy of antihistamines for prevention of BA in children with AD or allergen sensitization showed some positive results [20], but this treatment is not accepted widely as a standard because of the risk of adverse events, particularly when taken over a long period. Effective treatment with safe medication to improve scratching and skin sensitization, even if not treating the underlying disease, may be useful for preventing onset of AR in patients with AD.

The results of our prospective study indicate that preventing an increase of HDM-specific IgE and sensitization to HDM are likely to be beneficial interventions for prevention of AR and BA, respectively, and effective control of AD would be prevention of AR. The beneficial

interventions for reducing development of AR are also effective for the prevention of subsequent onset of BA. We note that these results are based on a relatively small number of patients, and further large-scale studies are needed to clarify these important issues.

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