
Correlates of outcome for atopic dermatitis

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Background: The worldwide incidence and prevalence of atopic dermatitis (AD) are increasing. Few good studies have addressed AD in terms of the factors affecting disease prognosis.

Objective: To identify significant correlates of persistent AD because this would be clinically valuable information.

Methods: Potential correlates of AD, including race, onset age, age of solid food introduction, breastfeeding, sinopulmonary infections, other atopic diseases, peripheral eosinophilia, total IgE level, and eosinophilic cationic protein levels, were investigated in 177 patients aged 5 to 18 years. Correlates were compared with AD remission vs nonremission status.

Results: A total of 133 patients (75.1%) were not in remission at the age of 5 years or older and were, thus, classified as having persistent AD. Patients with histories of peanut allergy (odds ratio [OR], 2.92; 95% confidence interval [CI], 1.30–6.55), egg allergy (OR, 2.71; 95% CI, 1.17–6.30), or dust mite allergy (OR, 4.02; 95% CI, 1.84–8.82) were significantly more likely to have persistent AD than those without these factors. There was a trend toward increased odds of persistence in those with peripheral eosinophilia ($P = .06$) and decreased odds of persistence in those with frequent sinopulmonary infections (OR, 0.51; 95% CI, 0.25–1.03).

Conclusions: Egg, peanut, and dust mite allergies are significant correlates of AD persisting beyond school age. There may also be increased odds in those with peripheral eosinophilia and decreased odds in those with frequent sinopulmonary infections. This highlights the importance of assessing these correlates in patients with AD and modifying the correlates that can be modified. Further studies on whether modification of these correlates and/or early aggressive AD management improves outcome are needed.

Ann Allergy Asthma Immunol. 2009;103:146–151.

INTRODUCTION

Atopic dermatitis (AD) is the most common dermatitis in childhood. It typically begins in infancy and has a variable prognosis, either lasting into adulthood or resolving in the first several years of life.^{1–3} It is also considered to be one of the first manifestations of atopy.⁴ Although considered a “minor” diagnosis by most physicians, it has a significant effect on patient quality of life; may lead to more “serious” diseases, such as asthma; and has a substantial economic effect on both affected individuals and the general population.⁵ In addition, the worldwide incidence and prevalence of AD, and other atopic diseases, have been steadily increasing during the last 4 decades, with some studies showing a prevalence rate for AD in childhood of 10% to 15%.^{2,6–8}

Despite these data, there are few good studies addressing AD in terms of the factors affecting disease severity and prognosis. Most of the work exploring the natural history of AD has been done in Europe, and the results of these studies have been quite variable. This variability results from a lack of consensus on an operative definition of AD, the lack of a uniform and reliable tool for severity evaluation, and the low

importance ascribed to this disease by those who make public health policies.

Some of the proposed factors influencing AD prognosis include age of onset, family history, development of asthma or allergic rhinitis, total IgE level, and timing of flexural involvement.^{3,5,9} The purpose of this study is to investigate the natural course of AD and to explore the factors influencing persistence of AD beyond early school age. By doing so, we hope to provide a framework that will lead to the following: (1) increased awareness of the correlates of AD persistence and (2) the development of a comprehensive plan to control or modify these correlates, which may ultimately help improve long-term prognosis.

METHODS

This study was performed with the approval of the institutional review board of the Alfred I. duPont Hospital for Children, Wilmington, Delaware. The informed consent requirement was waived because the study posed minimal risk to the participants.

Study Population

We reviewed the medical records of all children with a diagnosis code of AD who were initially seen at our hospital's allergy or dermatology outpatient clinics between January 1, 1994, and August 1, 2008. Inclusion criteria were current age of 5 to 18 years and a diagnosis of AD by the allergy-immunology or dermatology outpatient clinics at our hospital or its satellite offices. Exclusion criteria were a duration of AD of less than 3 months, eczema other than AD, immunodeficiency, and no documented skin examination for

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Disclosures: Authors have nothing to disclose.

Received for publication November 26, 2008; Received in revised form February 16, 2009; Accepted for publication March 14, 2009.

1 year (the latter group was considered unavailable for follow-up). A total of 177 patients were eligible for the study by the criteria listed. The average age of the patients at data analysis was 9.1 years.

Historical information for these 177 patients was gathered by both medical record review and parental questioning in the office, regarding age of disease onset, race, distribution of lesions at onset, breastfeeding, age of solid food introduction, presence of asthma, number of sinopulmonary infections per year, and food and environmental allergies.

Patients were divided into 2 groups based on remission status at the age of 5 years or older ("persistent AD" indicated those not in remission, and "nonpersistent AD" indicated those in remission). *Remission* was defined as 2 normal skin examination results within a 6-month period, without the use of rescue medications, or a follow-up visit in any department within 1 year of the last allergy or dermatology visit, documenting no AD flares or need for rescue medication in the interval.

Demographic Data

Patients were divided into 2 groups for analysis: onset when younger than 1 year or onset when 1 year or older. For race, patients were coded as African American, white, and other. The category "other" comprised patients of Asian, Indian, Hispanic, and multiracial backgrounds. This was done because of low patient numbers in each of these racial groups.

Data on Laboratory Studies and Sinopulmonary Infections

Laboratory studies were reviewed for the presence of peripheral eosinophilia at any time and for total IgE and eosinophilic cationic protein (ECP) levels. If there was more than 1 value for any test, the highest value was recorded. Each of these laboratory values was then coded as either elevated or normal for statistical analysis.

The frequency per year of otitis media, acute sinusitis, bronchitis treated with antibiotics, or pneumonia was determined, and patients were then grouped as having either 3 or fewer infections per year or more than 3 infections per year.

Food and Environmental Allergies

Patients with appropriate clinical histories underwent skin prick testing (SPT), IgE blood testing (ImmunoCAP; Phadia AB, Uppsala, Sweden), or both, performed to environmental or food allergens or both. Environmental testing consisted of a panel of the most common indoor and outdoor aeroallergens in our geographic area (grass mix, Bermuda grass, weed mix, ragweed mix, tree mix, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, dog, cockroach, mold mix, *Aspergillus fumigatus*, *Alternaria*, *Hormodendrum* or *Cladosporium*, and penicillium). Outdoor allergen testing was performed only on children 2½ years or older.

In patients younger than 5 years with significant AD, SPT was performed to egg, milk, soy, and wheat. Additional foods or aeroallergens were tested on any patient based on history or parental concern.

For all except 5 patients, a diagnosis of food allergy was made using the following criteria: (1) history of adverse reaction to food; (2) food specific IgE levels greater than 95% the positive predictive value (PPV) to egg, milk, peanut, or fish; and (3) an SPT result of 3 mm greater than control.¹⁰⁻¹²

In some cases, a patient could not undergo SPT because of either inability to discontinue antihistamine use or severe AD. Therefore, IgE blood testing was performed to food, aeroallergens, or both; any value greater than 0.35 kU/L for aeroallergens and greater than or equal to the 95% PPV for food allergens was considered positive.¹³

Asthma

Patients were considered to have asthma based on National Institutes of Health criteria of history of cough, especially worse at night, recurrent wheezing, difficulty breathing, or chest tightness, which occur with or are worsened by exercise, viral infections, inhalant allergens, irritant exposure, change in weather, strong emotions, stress, or menses.¹⁴ Patients were also considered to have asthma if there was a history of physician-diagnosed asthma.

Other Variables

Determination of distribution of lesions at onset was based on the answer to the following question, "When the eczema began, what areas did it first affect?" Patients were then grouped into flexure involvement at onset or no flexure involvement at onset. Breastfeeding was coded as either "yes" or "no," independent of the duration or formula supplementation. The age at introduction of solids was initially gathered as numerical data, and then patients were grouped as introduction at younger than 6 months or at 6 months or older.

Statistical Analysis

The distributions of pediatric patients with persistent AD and nonpersistent AD by the age of 5 years were presented using frequencies and percentages for all categorical variables (Table 1). The association of the nonpersistence of AD by the age of 5 years and predictor variables was evaluated using an unconditional univariable logistic regression model (Table 1). A stepwise logistic regression procedure was performed to select the variables that contribute significantly in persistence of AD. Variables with many missing values or with an odds ratio (OR) close to 1.0 in univariate analysis, such as flexure onset, breastfed, solid food introduction, peripheral eosinophilia, elevated serum ECP level, and elevated total serum IgE level, were not included for this analysis. $P = .05$ was set as the entering criterion into the model.

All analyses were 2-tailed at the $P < .05$ significance level. Analyses were performed based on the available data only. Statistical package SPSS, version 14.0 (SPSS Inc, Chicago, Illinois), was used for all analyses.

RESULTS

Of the 177 patients, 133 (75.1%) had persistent disease and 44 (24.9%) were in remission based on our definition. De-

Table 1. Univariable Logistic Regression Model to Examine the Association of Persistence of AD With Potential Correlates

Variable	Type of AD		Odds ratio (95% confidence interval)
	Persistent (not in remission)	Nonpersistent (in remission)	
Age of onset, y			
<1 (n = 124)	94 (75.8)	30 (24.2)	1.00 ^a
≥1 (n = 53)	39 (73.6)	14 (26.4)	0.89 (0.43–1.86)
Race			
African American (n = 64)	48 (75.0)	16 (25.0)	1.00 ^a
White (n = 80)	57 (71.2)	23 (28.8)	0.83 (0.39–1.74)
Other (n = 33)	28 (84.8)	5 (15.2)	1.87 (0.62–5.65)
Flexure onset			
No (n = 79)	57 (72.2)	22 (27.8)	1.00 ^a
Yes (n = 57)	44 (77.2)	13 (22.8)	1.37 (0.59–2.88)
Breastfed			
No (n = 42)	29 (69.0)	13 (31.0)	1.00 ^a
Yes (n = 83)	61 (73.5)	22 (26.5)	1.24 (0.55–2.81)
Solid food introduction age, mo			
<6 (n = 48)	34 (70.8)	14 (29.2)	1.00 ^a
≥6 (n = 55)	40 (72.7)	15 (27.3)	1.10 (0.47–2.60)
Asthmatic			
No (n = 46)	34 (73.9)	12 (26.1)	1.00 ^a
Yes (n = 131)	99 (75.6)	32 (24.4)	1.09 (0.51–2.36)
Sinopulmonary infections per year			
<3 (n = 116)	92 (79.3)	24 (20.7)	1.00 ^a
≥3 (n = 59)	39 (66.1)	20 (33.9)	0.51 (0.25–1.03)
Peripheral eosinophilia			
No (n = 70)	50 (71.4)	20 (28.6)	NA
Yes (n = 10)	10 (100.0)	0	NA
Elevated serum ECP level			
No (n = 6)	5 (83.3)	1 (16.7)	1.00 ^a
Yes (n = 18)	17 (94.4)	1 (5.6)	3.40 (0.18–64.68)
Elevated total serum IgE level			
No (n = 31)	26 (83.9)	5 (16.1)	1.00 ^a
Yes (n = 40)	35 (87.5)	5 (12.5)	1.35 (0.35–5.14)
Egg allergy			
No (n = 119)	83 (69.7)	36 (30.3)	1.00 ^a
Yes (n = 58)	50 (86.2)	8 (13.8)	2.71 (1.17–6.30)
Milk allergy			
No (n = 150)	109 (72.7)	41 (27.3)	1.00 ^a
Yes (n = 27)	24 (88.9)	3 (11.1)	3.01 (0.86–10.53)
Wheat allergy			
No (n = 166)	125 (75.3)	41 (24.7)	1.00 ^a
Yes (n = 11)	8 (72.7)	3 (27.3)	0.88 (0.22–3.45)
Soy allergy			
No (n = 159)	118 (74.2)	41 (25.8)	1.00 ^a
Yes (n = 18)	15 (83.3)	3 (16.7)	1.74 (0.48–6.31)
Peanut allergy			
No (n = 111)	76 (68.5)	35 (31.5)	1.00 ^a
Yes (n = 66)	57 (86.4)	9 (13.6)	2.92 (1.30–6.55)
Tree nut allergy			
No (n = 156)	114 (73.1)	42 (26.9)	1.00 ^a
Yes (n = 21)	19 (90.5)	2 (9.5)	3.50 (0.78–15.68)
Shellfish allergy			
No (n = 163)	122 (74.8)	41 (25.2)	1.00 ^a
Yes (n = 14)	11 (78.6)	3 (21.4)	1.23 (0.33–4.64)

Abbreviations: AD, atopic dermatitis; ECP, eosinophilic cationic protein.

^a Reference.

Table 1. Continued

Variable	Type of AD		Odds ratio (95% confidence interval)
	Persistent (not in remission)	Nonpersistent (in remission)	
Cat allergy			
No (n = 104)	76 (73.1)	28 (26.9)	1.00 ^a
Yes (n = 72)	56 (77.8)	16 (22.2)	1.29 (0.64–2.61)
Dog allergy			
No (n = 136)	99 (72.8)	37 (27.2)	1.00 ^a
Yes (n = 40)	33 (82.5)	7 (17.5)	1.76 (0.72–4.33)
Dust mite allergy			
No (n = 94)	60 (63.8)	34 (36.2)	1.00 ^a
Yes (n = 81)	71 (87.7)	10 (12.3)	4.02 (1.84–8.82)
Weed allergy			
No (n = 124)	92 (74.2)	32 (25.8)	1.00 ^a
Yes (n = 51)	39 (76.5)	12 (23.5)	1.13 (0.53–2.42)
Tree allergy			
No (n = 119)	86 (72.3)	33 (27.7)	1.00 ^a
Yes (n = 56)	45 (80.4)	11 (19.6)	1.57 (0.73–3.40)
Grass allergy			
No (n = 117)	87 (74.4)	30 (25.6)	1.00 ^a
Yes (n = 58)	44 (75.9)	14 (24.1)	1.08 (0.52–2.25)
<i>Alternaria</i> allergy			
No (n = 142)	104 (73.2)	38 (26.8)	1.00 ^a
Yes (n = 33)	27 (81.8)	6 (18.2)	1.64 (0.63–4.29)
<i>Aspergillus</i> allergy			
No (n = 150)	112 (74.7)	38 (25.3)	1.00 ^a
Yes (n = 25)	19 (76.0)	6 (24.0)	1.07 (0.40–2.89)

mographic data for each of these groups are given in Table 1. There were no significant differences between the groups based on age of onset, race, flexure involvement at onset, breastfeeding, or concomitant asthma diagnosis. Table 1 also shows data for specific food and environmental allergies for each group. Both peanut allergy (OR, 2.92; 95% confidence interval [CI], 1.30–6.55) and egg allergy (OR, 2.71; 95% CI, 1.17–6.30) were significantly associated with increased odds of persistence, as was dust mite allergy (OR, 4.02; 95% CI, 1.84–8.82). There is a trend, although not quite statistically significant, toward increased odds of persistence in patients with peripheral eosinophilia ($P = .06$) and toward almost half the decreased odds of persistence in patients with more than 3 sinopulmonary infections per year (OR, 0.51; 95% CI, 0.25–1.03). There were no other individual food or environmental allergies that were significantly associated with persistent disease.

Finally, in the stepwise forward selection method, dust mite allergy (OR, 3.68; 95% CI, 1.66–8.15) and peanut allergy (OR, 2.63; 95% CI, 1.14–6.04) remained as significant factors for the persistence of AD.

DISCUSSION

The percentage of persistence of AD was 76% in our study. Although some studies have shown lower persistence percentages, others have shown similar values to ours. In a longitudinal study of 40 children with AD observed for more

than 10 years, Linna et al¹⁵ found that 18% had complete AD remission, whereas 65% had decreased disease severity. Kissling and Wuthrich¹⁶ described 47 patients diagnosed as having AD by the age of 2 years and found that 20 years later, 72% still had signs of AD. A recent study from our own hospital also showed 75% persistence of AD, using the same definition of remission.¹⁷ The differences in persistence percentages are most likely because of the different definitions of remission and the difference in the age until which patients were observed.

Our study identified several correlates for increased odds of persistence of AD by school age: egg, peanut, and dust mite allergy. There is also a suggestion that the presence of peripheral eosinophilia predisposes patients to increased odds of persistence. Other studies have uncovered similar prognostic factors. A 2006 study from Italy of more than 200 children showed a significant prolongation of AD with egg allergy.¹⁸ A population cohort study of 981 children in the United Kingdom found that at the age of 4 years, the greatest independent risk factor for AD was peanut sensitization.¹⁹ A recent study from our own hospital showed significant associations of many factors.²⁰ Borres et al²¹ found that current or future atopic disease development was associated with peripheral eosinophilia at the age of 3 months. Peripheral eosinophilia was significantly correlated with disease activity in the study of Kagi et al²² on markers of clinical activity of AD. A large cohort study of German children older than 7 years

identified more severe AD, food allergy (especially to less prevalent foods, such as wheat and soy), having 2 or more atopic family members, and early wheeze as indicators of poorer prognosis for AD. They found no association with onset at younger than 1 year, sex, breastfeeding, age at solid food introduction, parental smoking, or number of infectious diseases.²

Our study did not show any association of asthma with persistence of AD. This finding has also been reported in multiple studies on AD.^{17,23} Again, the variability in these studies results from the use of different definitions of AD, nonstandardized methods for determining disease severity and remission, and differences in the definitions of the variables investigated.

There was a trend toward an inverse relationship between AD persistence and the frequency of sinopulmonary infections in early childhood. The few studies that have examined this predictor showed no significant effect.^{2,5} However, sinopulmonary infections, such as those comprising our definition (otitis media, acute sinusitis, bronchitis treated with antibiotics, or pneumonia), may be taken as a marker of "hygiene" status. If the hygiene hypothesis is correct, then having more frequent infections (ie, less hygiene) should have a protective effect on atopic disease. In addition, these types of infections help induce a T_H1-biased immunity, thereby preventing, or lessening, the induction of the T_H2 system that causes atopy.

This study has some limitations. First, given the retrospective nature of the study, certain demographic data were missing from many patients, decreasing the effective sample size for those factors. Therefore, we may have overlooked some significant associations. For example, the number of patients with available ECP levels is small, but the data suggest that an elevated ECP level might have been found to be a significant correlate had the "n" value been larger.

Second, some data relied on parental or patient recall; however, this is consistent with the situation in clinical practice because the information obtained during an office visit history also relies on recall.

Third, our study population consists of patients referred to our tertiary care center by community physicians, which could lead to our having a skewed population of more severely affected patients. However, it is common practice for the primary care physicians in our area to refer patients with even mild disease for allergy evaluation. Also, some patients are referred for other reasons and happen to have a concomitant history of, or current, AD.

Finally, with regard to the criteria for diagnosing food allergy, there were only 5 patients for whom a positive IgE blood test value of 95% PPV or greater was the sole evidence for labeling them as having a food allergy. This is unlikely to affect the results meaningfully.

In conclusion, we observed an increased odds of persistence of AD after 5 years of life among children with a history of allergy to egg, peanut, and dust mite. There may

also be an increased odds of persistence in those with peripheral eosinophilia.

An enhanced understanding of these important correlating factors is a key to developing optimal methods of preventing or modifying the course of this disease. This may also have an effect on the future development of asthma and allergic rhinitis. It will be important to perform further prospective studies on whether modification of the correlates, early aggressive AD management, or both improve outcome.

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