

Correlation between age and allergens in pediatric atopic dermatitis

I-Jen Wang, MD*†; Yu-Tsan Lin, MD†; Yao-Hsu Yang, MD†; Chi-Ling Chen, PhD‡; Ya-Huei Tsai, MD*; Bor-Luen Chiang, MD, PhD†; and Kung-Chang Hwang, MD*

Background: There has been significant progress recently in the clinical investigation of atopic dermatitis (AD), especially in the recognition of aeroallergens as aggravating factors in AD. However, sensitization to food allergens and aeroallergens in children with AD has not been fully studied.

Objective: To evaluate the correlation between age and allergens in children with AD.

Methods: A retrospective cross-sectional study was performed between January 1, 1999, and December 31, 2002, on 262 children with a definitive diagnosis of AD aged 0 to 16 years. Comparison of 3 age groups (<2 years, 2–5 years, and >5 years) with the correlation of food allergens and aeroallergens using the CAP-FEIA test was made using linear regression and logistic regression analyses.

Results: In children younger than 2 years, AD was associated with food allergens. In children aged 2 to 5 years, both food allergens and aeroallergens played an important role. In children older than 5 years, only elevated aeroallergen specific IgE levels were noted ($P < .02$). Age correlated negatively with food allergens and positively with aeroallergens after adjusting for sex ($P < .04$). Sensitization to aeroallergens may correlate with acquisition of the respiratory symptoms of the atopic state.

Conclusions: Food allergens may be the major trigger of AD in early life, after which the role of environmental aeroallergens become more important and may be associated with respiratory sensitization.

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INTRODUCTION

Atopic dermatitis (AD) is a chronic skin disorder of early infancy, childhood, and adolescence that is frequently associated with elevated serum IgE levels and a personal or family history of AD, allergic rhinitis, or bronchial asthma.¹ The cause of allergy is multifactorial, and the development of AD seems to be due to the interaction between genetic factors and several environmental factors. The latter includes inhalants and food allergens.² The variant that is usually called *extrinsic AD* is associated with the elevation of allergen specific IgE antibody levels in up to 80% of cases.³

The pattern of reactivity to ingested and inhaled allergens associated with age has been studied previously. Soothill et al⁴ observed an increasing prevalence of reactions to inhaled allergens with age. Samueli et al⁵ divided patients with AD into 3 groups according to age and found a high percentage of dust mite sensitization in the oldest group. A study by Foucard⁶ showed decreasing IgE levels to cow's milk and egg with increasing age. Orgel et al⁷ found that children younger than 12 months showed skin test reactivity more commonly to foods, particularly milk and eggs, whereas older children

reacted to inhalant antigens. Most of these studies examined only the allergens of milk, egg, and mite by skin testing.

In Far Eastern countries, many studies about allergen sensitization in asthma have been reported. However, allergen sensitization in AD has not been fully investigated. In addition, the role of aeroallergens in the development and aggravation of AD is also controversial. Therefore, the purpose of this study is to evaluate the association between age and sensitization to different food allergens and aeroallergens, including fungi, in children with AD. The severity of allergic diseases with allergen sensitization and the course of sensitization in AD were also studied.

METHODS

Patients

Between January 1, 1999, and December 31, 2002, children with AD aged 0 to 16 years ($n = 262$) were enrolled in this retrospective cross-sectional study. The diagnosis of AD was confirmed if the following were detected: pruritus, typical morphologic features and distribution, and a chronic relapsing course. Children were grouped by age at blood sampling (26 children <2 years, 135 children aged 2–5 years, and 101 children >5 years). Comparison of the 3 age groups with the correlation of food allergens and aeroallergens was made. Clinical evaluation of the severity of AD was performed using the severity scoring of AD (SCORAD) at the time of blood sampling.⁸ The range of SCORAD scores is 0 to 80. As proposed by the European Task Force for Atopic Dermatitis, eczema was graded as mild (SCORAD score, 0–15), moderate (SCORAD score, 16–40), and severe (SCORAD score, >40).

* Department of Pediatrics, Taipei Hospital, Department of Health, Taipei, Taiwan.

† Division of Allergy, Immunology, and Rheumatology, Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan.

‡ Institute of Epidemiology, College of Public Health, National Taiwan University, Taipei, Taiwan.

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A presumptive diagnosis of asthma was based on having had 4 or more attacks of wheezing in the past 12 months or 1 to 3 wheezing episodes in addition to night awakening for wheezing, nocturnal cough, and wheezing after exercise. A diagnosis of allergic rhinitis was founded on having had 1 or more of the following symptoms: sneezing, rhinorrhea, congestion, or nasal itch. The severity of asthma was graded by Global Initiative for Asthma guidelines as intermittent, mild persistent, moderate persistent, and severe persistent.

Definition of Allergic Sensitization

A child was described as being sensitized to aeroallergens if the specific IgE level was elevated for at least 1 of 5 tested allergens: *Dermatophagoides pteronyssinus* (Der p 1), *Dermatophagoides farinae* (Der f 1), cockroaches, animal danders, and *Aspergillus*. A child was considered to have food allergen sensitization if specific IgE was detectable for at least 1 of 6 common allergens in Taiwan (milk, shrimp, egg yolk, egg white, peanuts, and soybeans) using the CAP-FEIA test (Pharmacia, Uppsala, Sweden). Only a CAP-FEIA class of 2 or higher or a concentration of allergen specific IgE greater than 0.7 kIU/L was considered positive for this study. A total IgE level greater than 200 kIU/L was considered to be elevated. The sensitivity and specificity of the CAP-FEIA test were 0.93 and 0.89, respectively (according to Pharmacia). The positive and negative predictive values were 0.93 and 0.88, respectively, which might be affected by the prevalence of AD.

Statistical Analysis

Logistic regression analysis was conducted to estimate, by means of the odds ratio, the relative risk in the 3 age groups associated with each food allergen and aeroallergen. Furthermore, the relative risk of asthma and allergic rhinitis associated with 6 CAP-FEIA classes of the aeroallergens Der p 1, Der f 1, cockroaches, and *Aspergillus* was also evaluated. Sex-adjusted odds ratios of allergens are presented in the final model.

Linear regression models were also performed, with changes in food allergens, aeroallergens, asthma, allergic rhinitis, and IgE level as independent variables and age as a dependent variable. The sex-adjusted coefficient is presented in the final model. $P < .05$ was set to be against the null hypothesis. Analyses were conducted using Stata version 6.0 (Stata Corp, College Station, TX).

RESULTS

Of 262 children with a definitive diagnosis of AD, 144 (55%) were boys and 118 (45%) were girls. Overall, 142 children (54%) had a family history of atopy, 79 (30%) combined with asthma and 141 (54%) combined with allergic rhinitis. Elevated IgE levels (>200 kIU/L) were found in 150 patients (57%), and eosinophilia (eosinophil count $>5\%$ of the total white blood cell count) was noted in 79 patients (30%). One hundred children (38%) had been weaned from breastfeeding before the age of 6 months, and 134 (51%) were fed with common infant formula. The foods most often incriminated

were eggs (both egg white and egg yolk) in 64 patients (24%), milk in 49 (19%), shrimp in 35 (13%), peanuts in 17 (6%), and soybeans in 11 (4%). The aeroallergens incriminated were Der p 1 in 81 patients (31%), Der f 1 in 79 (30%), animal danders in 32 (12%), cockroaches in 29 (11%), and *Aspergillus* in 10 (4%). Milk sensitization is often combined with egg white sensitization ($P < .01$ [data not shown]). Elevation of the peanut allergen specific IgE level seldom existed alone and was often combined with elevations of other food allergens. Whereas cow's milk and hen's eggs have been identified as important triggers in infants, foods such as peanuts and shrimp have a greater impact in adolescents and adults. In children with AD who have a food sensitization, 61% had concomitant urticaria. Fifty-five percent of patients with elevated food allergen specific IgE levels had a positive reaction to an open food challenge. The positive rate of specific IgE to milk and egg decreased gradually with age, whereas the positive rate to mites, animal danders, and cockroaches increased with age. This was compatible with the results of skin testing, which was performed in 39 patients (15%). Of 81 patients (31%) who underwent the evaluation of SCORAD, 15 (19%) were graded as mild, 45 (55%) as moderate, and 21 (26%) as severe. The ratio of patients with severe SCORAD scores (score >40) was higher in the group with elevated allergen specific IgE levels against food allergens and aeroallergens than in the group with normal IgE levels ($P < .03$). The ratio of patients who also had severe asthma was also statistically significantly higher.

The mean $\pm$ SE patient age was 1.2 ± 0.9 years at diagnosis and 4.8 ± 3.8 years at blood sampling. In the 26 patients with AD younger than 2 years (10%), AD was strongly associated with food allergens using odds ratios after adjusting for sex. In the 135 patients aged 2 to 5 years (52%), both food allergens and aeroallergens played an important role. In the 101 patients older than 5 years (38%), AD was significantly correlated with aeroallergens ($P < .02$). Asthma and allergic rhinitis were associated with older age (Table 1). Twenty-one patients (8%) underwent the CAP-FEIA test twice, with a mean $\pm$ SE interval of 18.3 ± 5.4 months between tests. Nine (43%) of these 21 patients developed aeroallergen sensitization, 6 (28%) developed both food allergen and aeroallergen sensitization, 4 (19%) developed food allergen sensitization, and 2 (10%) did not develop any sensitizations.

Linear regression analysis revealed that age as a dependent variable was negatively correlated with food allergens, except shrimp, and positively correlated with aeroallergens, asthma, and allergic rhinitis ($P < .04$) after adjusting for sex. Total IgE level increased with age but only with marginal statistical significance (Table 2). In addition, age was not positively correlated with each allergen specific IgE. The older the patient with AD, the greater the association of the aeroallergen sensitization and the greater the risk of combining with allergic rhinitis and asthma.

The higher the class of the CAP-FEIA test of aeroallergen specific IgE for Der p 1, Der f 1, cockroaches, and *Aspergil-*

Table 1. Food Allergens and Aeroallergens in 262 Children with Atopic Dermatitis by Age Group*

	Sex-adjusted OR (95% CI)		
	<2 y (n = 26)†	2–5 y (n = 135)‡	>5 y (n = 101)§
Food allergen	2.58 (1.07–6.21)	1.09 (0.58–2.05)	0.57 (0.29–1.13)
Aeroallergen			
Der p 1	0.02 (0.002–0.142)	0.72 (0.44–1.91)	4.28 (2.41–7.59)
Der f 1	0.02 (0.003–0.159)	0.72 (0.44–1.18)	4.02 (2.30–7.05)
Cockroach	¶	0.45 (0.18–1.10)	3.53 (1.45–8.61)
Asthma	¶	0.58 (0.34–0.99)	3.26 (1.88–5.65)
Allergic rhinitis	0.05 (0.01–0.24)	0.55 (0.33–0.90)	4.63 (2.65–8.09)

Abbreviations: OR, odds ratio; CI, confidence interval; Der p 1, *Dermatophagoides pteronyssinus*; Der f 1, *Dermatophagoides farinae*.

* Egg yolk, egg white, peanut, milk, shrimp, and *Aspergillus* are not listed because they are not statistically significant.

† Compared with ≥2-year-olds.

‡ Compared with <2-year-olds and >5-year-olds.

§ Compared with ≤5-year-olds.

|| $P < .05$.

¶ No children younger than 2 years.

Table 2. Results of Linear Regression Analysis in 262 Children with Atopic Dermatitis*

	Sex-adjusted coefficient†
Food allergen	
Egg yolk	−0.68
Egg white	−1.18‡
Peanut	−0.33
Milk	−0.12
Shrimp	0.56‡
Aeroallergen	
Der p 1	0.71‡
Der f 1	0.71‡
Cockroach	−1.27‡
<i>Aspergillus</i>	1.12‡
Asthma	2.77‡
Allergic rhinitis	3.00‡
IgE	0.003

Abbreviations: Der f 1, *Dermatophagoides farinae*; Der p 1, *Dermatophagoides pteronyssinus*.

* Food allergens, aeroallergens, asthma, allergic rhinitis, and IgE are independent variables, and age is the dependent variable.

† Regression coefficients significantly different from 0.

‡ $P < .05$.

lus, the higher the risk of asthma and allergic rhinitis using sex-adjusted odds ratios ($P < .005$ for trend). However, the classes of aeroallergen specific IgE were not positively correlated with the severity of asthma. Sensitization to aeroallergens may correlate with the acquisition of the respiratory symptoms of the atopic state (Table 3).

DISCUSSION

Food plays an important role in the unpredictable and irregular aggravation of skin lesions in patients with AD. In 1 study,⁹ exclusion of the offending foods for 3 months brought about progressive improvement in the disease. However, the

Table 3. Correlation of Children with Atopic Dermatitis Sensitized to Aeroallergens (*Dermatophagoides farinae*) with Asthma

CAP-FEIA Class	Asthma, No. (%)		Sex-adjusted OR (95% CI)
	No (n = 182)	Yes (n = 79)	
0	103 (57)	1 (1)	1
1	7 (4)	0	...
2	8 (4)	2 (3)	23.15 (1.88–285.85)*
3	15 (8)	7 (9)	32.07 (3.54–290.17)*
4	37 (20)	45 (57)	96.08 (12.63–731.18)*
5	2 (1)	8 (10)	314.71 (25.26–3,921.49)*
6	10 (5)	16 (20)	126.23 (14.91–1,069.01)*
P for trend	...	...	<.005

Abbreviations: CI, confidence interval; OR, odds ratio.

* $P < .05$.

clinical investigation of patients with AD has made a great deal of progress recently, especially in the recognition of the importance of aeroallergens in the aggravation of AD. It is known that these allergens can unleash hypersensitivity responses through inhalation or contact with the skin.¹⁰ Children with AD, presenting with an altered barrier, have enhanced percutaneous penetration by the aeroallergens, which bind to IgE on the Langerhans cells. The Langerhans cells then present the allergens to the T cells, which induce a delayed inflammatory response. The T cells, by releasing cytokines, may also play a role in the induction or regulation of IgE production by B cells, causing an elevation of IgE levels. By entering the skin through the circulation, aeroallergens can induce delayed skin reactions.¹¹

In the present study, AD was associated with food allergens in patients younger than 2 years. The positive rate of specific IgE to milk and egg decreased gradually with age, which implies that sensitivity to food allergens decreases and becomes clinically tolerant with age. This does not mean that aeroallergens such as mites have nothing to do with AD at a

younger age but that they have different mechanisms of hypersensitivity compared with the older group. There were still 6 (23%) of 26 children younger than 2 years who were sensitized to the aeroallergens Der p 1, Der f 1, cockroaches, and *Aspergillus*. Varela et al¹² found that sensitivity to mite antigens was found in 20% to 60% of patients when immediate hypersensitivity was evaluated by the detection of IgE antibodies and skin prick testing and in 30% to 50% of patients when delayed hypersensitivity was studied using patch testing. There was a positive association between the younger age groups and delayed hypersensitivity, whereas the opposite was true for immediate hypersensitivity.¹² Our study was evaluated by the detection of IgE specific antibodies and immediate hypersensitivity to Der p 1 and Der f 1. Fewer associations with aeroallergen specific IgE in the younger group were found.

Skin prick tests are more sensitive than CAP-FEIA tests.¹³ However, we chose the CAP-FEIA test to detect allergen specific IgE in this study because of its specificity, convenience, and ability to quantify the concentration. Skin tests were performed in 39 (15%) of the 262 patients in our study, which was compatible with the CAP-FEIA test. Van Asperen et al¹⁴ found that skin test reactions to ingested allergens developed in early infancy and were usually transient and that skin test reactions to Der p 1 that occurred in later infancy were persistent and increased with age. These findings are consistent with the increasing aeroallergen specific IgE level with age and its association with asthma and allergic rhinitis in our study.

Breastfeeding for a least 4 to 6 months, stepwise introduction of solid food only after this age, and avoidance of highly allergenic foods during the first year of life have been documented to prevent food sensitization.¹⁵ However, our patients rarely breastfed for longer than 6 months. It was crucial to ask whether a low percentage of breastfeeding accounts for the high prevalence of AD in Taiwan (21.4%)² or whether there is selection bias because our patients were sampled from a medical center. Although selection bias was hard to avoid in this hospital-based study, the prevalence of AD decreased after encouraging breastfeeding in 2 recent years. Our study also delineated decreasing milk allergen specific IgE levels with age. Oral tolerance or increasing T regulatory cells and decreasing milk intake with age might account for this phenomenon. Another interesting finding was that milk allergen sensitization was often combined with egg white allergen sensitization in our study. It was important to clarify whether a molecular mimicry or cross-reaction of each allergen occurred in the allergen test. The allergenicity of lipocalins may be a consequence of molecular mimicry between lipocalin allergens and endogenous lipocalins at the T-cell level.¹⁶ Animal dander sensitization was usually detected in conjunction with mite allergen sensitization. The possible explanation was that animal danders might live with mites on pet hair. Peanuts rarely played a single allergen and were often combined with other food allergens. This may be because peanut sensitization developed later in childhood and

many food allergens had been sensitized by then. In addition, fungus aeroallergens have not previously been deemed to be important and were often thought to be related only to asthma and allergic rhinitis. However, fungus allergens might play a role in contributing to AD in our study, and sensitization to fungus was also increasing with age. More and more studies indicate the important roles of fungi in triggering and aggravating AD.¹⁷ Fungi were particularly significant in Taiwan because of its humid climate.

Food allergens may be the major trigger of AD in early life, after which the role of environmental aeroallergens becomes more important in the maintenance of AD later in life.¹⁸ So, environmental cleaning for AD prevention is also very important. Some studies reported that long-lasting sensitization to food allergens during the first 2 years of life with AD in early infancy have been found to be predictors of allergic airway disease later in childhood and the indicator of the allergic march.¹⁹ Whether the higher classes of the CAP-FEIA test of aeroallergens could predict the higher risk of developing respiratory symptoms of atopic disease at later ages and whether the course of sensitization changes over time from food allergens to aeroallergens could not fully be proven in our cross-sectional study. However, only a few studies have investigated many kinds of allergens, including fungi. Most studies have examined the allergens milk, egg, and mites only. Although we did not investigate all of the allergens in CAP-FEIA tests, each allergen we selected was the most common allergen and was likely to represent the food allergen and aeroallergen sensitization in childhood.

High total IgE levels had low predictive capacity for sensitization to aeroallergens. Elevated allergen specific IgE levels were previously thought to have no relation to the severity of the allergic status.²¹ However, in our study, the ratio of patients with AD with highly increased SCORAD scores was higher in the group with elevated allergen specific IgE levels. A time lag of elevation of IgE after allergen exposure might account for the discrepant results. In addition, only a small portion of children with AD underwent the SCORAD in this retrospective study, which might lead to selection bias or detection bias because physicians often performed SCORAD on more severe patients. We tried to keep the bias to a minimum by using statistical analyses. The higher classes of the CAP-FEIA test to aeroallergens, the higher the risk of combining respiratory allergy in patients with AD. By following up these children to the older age, the natural course of sensitization, its relationship with the severity of AD, and the development of clinical allergy will be investigated.

REFERENCES

1. Leung DY, Bieber T. Atopic dermatitis. *Lancet*. 2003;361:151–160.
2. Huang JL, Chen CC, Kuo ML, Hsieh KH. Exposure to a high concentration of mite allergen in early infancy is a risk factor for developing atopic dermatitis: a 3-year follow-up study. *Pediatr Allergy Immunol*. 2000;12:11–16.

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3. Werfel T, Kapp A. Environmental and other major provocation factors in atopic dermatitis. *Allergy*. 1998;53:731–739.
 4. Soothill JF, Stokes CR, Turner MW, Norman AP, Taylor B. Predisposing factors and the development of reaginic allergy in infancy. *Clin Allergy*. 1976;6:305–319.
 5. Samuelli S, Orsolini G, Migliaccio P, Baldini G, Paci A. Sensitization to house dust mites and juvenile atopic dermatitis. *Pediatr Med Chir*. 1994;16:247–249 [in Italian].
 6. Foucard T. A follow-up study of children with asthmatic bronchitis, I: skin test reactions and IgE antibodies to common allergens. *Acta Paediatr Scand*. 1973;62:633–644.
 7. Orgel HA, Kemp JP, Meltzer EO, Hamburger RN. Atopy and IgE in a pediatric allergy practice. *Ann Allergy*. 1977;39:161–168.
 8. European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis: the SCORAD index. *Dermatology*. 1993;186:23–31.
 9. Uenishi T, Sugiura H, Uehara M. Role of foods in irregular aggravation of atopic dermatitis. *J Dermatol*. 2003;30:91–97.
 10. Wananukul S, Huiprasert P, Pongprasit P. Eczematous skin reaction from patch testing with aeroallergens in atopic children with and without atopic dermatitis. *Pediatr Dermatol*. 1993;10:209–213.
 11. Novak N, Bieber T, Leung DY. Immune mechanisms leading to atopic dermatitis. *J Allergy Clin Immunol*. 2003;112(Suppl):S128–S139.
 12. Varela P, Selores M, Gomes E, et al. Immediate and delayed hypersensitivity to mite antigens in atopic dermatitis. *Pediatr Dermatol*. 1999;16:1–5.
 13. Kulig M, Bergmann R, Niggemann B, Burow G, Wahn U. Prediction of sensitization to inhalant allergens in childhood: evaluating family history, atopic dermatitis and sensitization to food allergens. The MAS Study Group (Multicentre Allergy Study). *Clin Exp Allergy*. 1998;28:1397–1403.
 14. Van Asperen PP, Kemp AS, Mellis CM. Skin test reactivity and clinical allergen sensitivity in infancy. *J Allergy Clin Immunol*. 1984;73:381–386.
 15. Boguniewicz M, Eichenfield LF, Hultsch T. Current management of atopic dermatitis and interruption of the atopic march. *J Allergy Clin Immunol*. 2003;112:S140–S150.
 16. Virtanen T, Zeiler T, Mantylarvi R. Important animal allergens are lipocalin proteins: why are they allergenic? *Int Arch Allergy Immunol*. 1999;120:247–258.
 17. Faergemann J. Atopic dermatitis and fungi. *Clin Microbiol Rev*. 2002;15:545–563.
 18. Guillet G, Guillet MH. Natural history of sensitizations in atopic dermatitis: a 3-year follow-up in 250 children: food allergy and high risk of respiratory symptoms. *Arch Dermatol*. 1992;128:187–192.
 19. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol*. 2003;112(Suppl):S118–S127.
 20. Rosario NA, Vilela MM. Quantitative skin prick tests and serum IgE antibodies in atopic asthmatics. *J Investig Allergol Clin Immunol*. 1997;7:40–45.
- Requests for reprints should be addressed to:
Bor-Luen Chiang, MD, PhD
Department of Pediatrics
National Taiwan University Hospital
7 Chung-Shan South Rd
Taipei 100, Taiwan
E-mail: gicmbor@ha.mc.ntu.edu.tw
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