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Original Article

Early-onset eczema is associated with increased milk sensitization and risk of rhinitis and asthma in early childhood

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Abstract *Background:* Atopic eczema and food allergy most commonly occur in the early childhood. However, the relationships between eczema onset and their relevance to the occurrence of atopic diseases relating to allergen sensitization remain unclear.

Methods: We investigated 186 children who were followed up regularly at the clinic for 4 years in a birth cohort study. The children were classified into three groups: early-onset eczema (<2 years old, n = 55), late-onset eczema (≥2 years old, n = 40), and never eczema groups (n = 91). The associations between the different onsets of eczema and total immunoglobulin E levels, absolute eosinophil count, sensitization to food and inhalant allergens, and allergic outcomes were assessed.

Results: A significantly higher prevalence of sensitization to food, especially milk was observed in children with early-onset eczema compared with those without eczema at age 1, 1.5, 2, 3, and 4 years. Furthermore, a significantly higher number of eosinophils was detected in children with early or late-onset eczema at the age of 1.5 years. Both the early- and late-onset eczema were

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significantly associated with a higher prevalence of allergic rhinitis at age 2, 3, and 4 years, and asthma at age 2. Moreover, the early-onset eczema group showed a significantly increased risk of allergic rhinitis ($P = 0.010$) and asthma ($P = 0.032$) at age 4.

Conclusion: The children with early-onset eczema (<2 years old) appear to be associated with an increased prevalence of milk sensitization and risk of rhinitis and asthma in early childhood.

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Introduction

Atopic eczema is the most prevalent allergic disease in children, affecting up to 30% of this population.¹ Eczema typically appears in infancy and tends to disappear at school age in over 70% of the cases.² In clinics, the association between eczema and other allergic diseases has been well documented. Furthermore, the sensitization to allergens is recognized as the most important factor for risk development of atopic diseases. However, a few studies have assessed the evidence for the allergic march between the atopic diseases in relation to allergen sensitization in early childhood.

Atopic eczema and food allergy commonly occur during the first 2 years of life with several evidence of temporal interrelation. Numerous studies have demonstrated that food allergens play an important role in triggering or exacerbating the severe forms of atopic eczema.³ The sensitization to food allergens occurs in early life and is a significant factor for infantile eczema.⁴ However, the prevalence of sensitization to food allergens decreases after 2 years of age, in parallel with the rising prevalence of sensitization to inhalant allergens at older age.^{4,5} In the early childhood, the relationship between eczema onset after infancy and allergen sensitization and their relevance to the occurrence of atopic diseases has not been well determined.

This study aimed to investigate the differences in early-onset (<2 years old) and late-onset (≥ 2 years old) eczema in children from a birth cohort in the Prediction of Allergies in Taiwanese Children (PATCH) study for a 4-year follow-up period. The associations between different onsets of eczema and atopic indices including total immunoglobulin E (IgE) levels, absolute eosinophil count (AEC), and sensitizations to food and inhalant allergens were assessed. Their relevance to the development of allergic rhinitis and asthma was also examined.

Methods

Study subjects

The PATCH study is an unselected, population-based prospective study to investigate the epidemiology and predictive factors of asthma and allergies in northern Taiwan. Children who were completed a 4-year follow-up in a birth cohort study were enrolled.⁶ Detailed descriptions about the recruitment of study subjects were described previously.⁴ This study was approved by the Ethics Committee of Chang Gung Memory Hospital (No. 102-1842C). All experiments in

this study were performed in accordance with the relevant guidelines and regulations and written informed consent was obtained from the parents or guardians of all study subjects.

Data collection

The parents or legal guardians of enrolled subjects were invited and requested to undergo an interview with experienced investigators answering a questionnaire derived from well-validated International Study of Asthma and Allergies in Childhood (ISAAC) at birth, 6 months, and 1, 2, 3, and 4 years of age.⁷ Detailed information regarding demographic data and confounding factors related to the development of atopic diseases including parental atopy, passive smoking, any older siblings, household income and infants sex, maternal and gestational age, and breastfeeding patterns were collected and analyzed.

Evaluation and diagnosis of atopic diseases

Information concerning current and past allergic symptoms for the diagnosis of atopic diseases was acquired from the modified ISAAC questionnaire.⁷ The phenotypes of atopic diseases were also evaluated by the same pediatric pulmonologist at the clinic. Diagnosis of atopic diseases including allergic rhinitis and asthma was described as in our previous study.^{8,9} Eczema was defined from questionnaire responses as scaly, red, itchy lesions involving the limbs, face, or trunk reported by the parents and diagnosed as eczema by the family doctor or consulted physician at clinic. Early-onset eczema, also known as infantile eczema, refers to eczema that occurs within the first 2 years of life; while eczema that manifests itself after the age of 2 is considered to be late-onset eczema.

AEC and serum allergen-specific IgE levels

A complete peripheral blood cell count was obtained using automated analysis, and the AEC was calculated. As described in our previous study,⁹ levels of total serum IgE were measured using ImmunoCAP (Phadia, Uppsala, Sweden), while allergen-specific IgE levels were determined using a commercial assay for IgE (ImmunoCAP Phadiatop Infant; Phadia) for a mix of the three most common food allergens (egg white, milk, and wheat) and inhalant allergens in Taiwan (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Cladosporium herbarum*).^{10,11} IgE

sensitization was defined as IgE levels ≥ 100 kU/L, while allergen sensitization was defined as values ≥ 0.35 kU/L.¹²

Statistical analysis

The detailed information and demographic data obtained through the questionnaire were collected and analyzed. Differences and comparisons of baseline characteristics and laboratory findings were performed with univariable parametric and nonparametric tests such as ANOVA, χ^2 , Fisher's exact test, and Kruskal–Wallis rank sum test. Multiple logistic regression analysis was used to determine the association between different onsets of eczema and allergic rhinitis and asthma by adjusting for confounding factors. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Statistics for Windows Version 20.0; Armonk, NY, USA), and graphs were drawn using GraphPad Prism software (GraphPad Software Inc. Version 5.01; San Diego, CA, USA). All statistical hypothesis tests were two-tailed and a *P* value < 0.05 was considered significant.

Results

Study population

A total of 258 children were recruited initially in this study, but 186 (72.1%) children who completed a 4-year follow-up period in the birth cohort were enrolled. No significant differences were observed in the baseline characteristics between the 258 and 186 children studied.⁹ Among the 186

children, 55 were diagnosed with early-onset eczema (<2 years old), and 40 were diagnosed with late-onset eczema (≥ 2 years old). At 4 years of age, atopic diseases, including eczema, rhinitis, and asthma were diagnosed in 21, 68, and 30 children, respectively. Table 1 shows the baseline characteristics of 186 children in relation to early- and late-onset eczema. The lower maternal age (*P* = 0.038) showed a borderline association with children with early-onset eczema, but no other significant difference was identified among different onsets of eczema.

Association between eczema and allergen sensitization

Fig. 1A shows the comparisons and differences between the different onsets of eczema and sensitization to allergens at different ages. The prevalence of food sensitization increased sharply after 6 months of age with a peak at age 2 and decreased markedly after 2 years old. A significantly higher prevalence of sensitization to food, especially milk, was found in children with early-onset eczema compared with children without eczema at ages 1, 1.5, 2, 3, and 4 years old. No significant difference was observed in the association between the different onsets of eczema and sensitization to other allergens, such as wheat and house dust mite allergens.

Association of eczema with AEC and IgE levels

Serum samples for AEC and IgE levels were collected and measured at 6 months and 1.5, 3, and 4 years old. Fig. 1B

Table 1 Baseline characteristics of 186 children in relation to different onsets of eczema for a 4-year follow-up period.

Characteristics	Eczema			P-value
	Never (n = 91)	Early-onset (n = 55)	Late-onset (n = 40)	
Family				
Maternal atopy	38 (42.2%)	23 (42.6%)	22 (55.0%)	0.364
Paternal atopy	48 (53.3%)	33 (61.1%)	21 (52.5%)	0.605
Passive smoking	48 (53.3%)	32 (58.2%)	18 (45.0%)	0.444
Any older siblings	49 (54.4%)	20 (36.4%)	17 (42.5%)	0.090
Household income				0.876
Low, ≤500,000 NTD	33 (36.7%)	21 (38.9%)	13 (32.5%)	
Medium, 500,000–1,000,000 NTD	38 (42.2%)	25 (46.3%)	19 (47.5%)	
High, >1,000,000 NTD	19 (21.1%)	8 (14.8%)	8 (20.0%)	
Infant				
Sex, male	45 (50.0%)	31 (56.4%)	25 (62.5%)	0.398
Maternal age (yr)	31.6 ± 4.3	29.8 ± 3.7	31.4 ± 4.6	0.038
Gestational age (wk)	37.9 ± 1.8	38.2 ± 2.4	38.3 ± 1.4	0.257
BMI (kg/m ²)				
Birth	12.4 ± 2.0	12.6 ± 2.1	12.7 ± 2.6	0.679
4 y/o	15.4 ± 1.95	15.8 ± 1.52	16.3 ± 1.94	0.159
Breastfeeding (first 6 months of life)				0.559
Exclusive	31 (34.1%)	16 (29.1%)	17 (42.5%)	
Partial	31 (34.1%)	21 (38.2%)	15 (37.5%)	
Formula	29 (31.9%)	18 (32.7%)	8 (20.0%)	
Hydrolyzed formula (ever)	10 (14.5%)	11 (22.4%)	7 (19.4%)	0.530
Episodes of respiratory diseases	38 (41.8%)	29 (52.7%)	19 (47.5%)	0.429
Antibiotics prescriptions	27 (37.0%)	30 (56.6%)	20 (50.0%)	0.081

Data shown are mean $\pm$ s.d. or number (%) of patients as appropriate. NTD, new Taiwan dollar; yr, year; wk, week; BMI, body mass index.

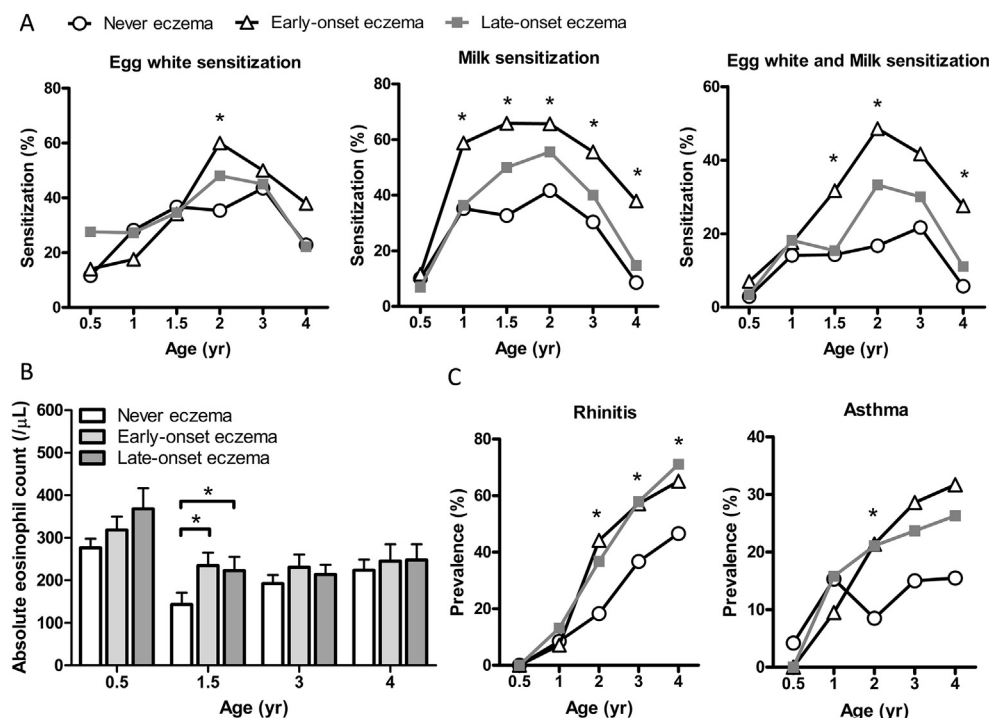


Figure 1. Early- and late-onset eczema and their relationships between allergen sensitization, absolute eosinophil count (AEC) and allergic respiratory diseases at different ages. Comparisons of different onsets of eczema with sensitization to egg white and milk (A), and AEC (B), and allergic rhinitis and asthma (C) at different years of age. Data shown are mean $\pm$ s.e.m. or percent of subjects as appropriate. *P*-values referred to the comparisons of sensitization to egg white at age 2 and milk at ages of 1, 1.5, 2, 3, and 4 years old (early-onset eczema vs. never eczema) are indicated by the marker. **P* < 0.05.

shows the comparisons and differences between the different onsets of eczema and AEC at different ages. A significantly higher number of eosinophils was detected in children with early or late-onset eczema compared with children without eczema at the age of 1.5 years. There was no significant difference in the association between eczema and IgE levels.

Association of eczema with allergic rhinitis and asthma

The prevalence of allergic rhinitis and asthma increased markedly since the age of 2 years. Fig. 1C shows the relationship between the different onsets of eczema and subsequent development of rhinitis and asthma at different ages. Compared with never eczema group, both early- and late-onset eczema were not only significantly associated with the higher prevalence of allergic rhinitis at 2, 3, and 4 years of age but also asthma at age 2. Furthermore, the early-onset eczema showed a significantly increased risk of allergic rhinitis [odds ratio (OR), 3.71; 95% confidence interval (CI), 1.37–10.02; *P* = 0.010] and asthma (OR, 3.80; 95% CI, 1.12–12.85; *P* = 0.032) at 4 years old (Table 2).

Discussion

The association between eczema onset and other atopic diseases relating to allergen sensitization in early childhood has not been fully clarified. This study has demonstrated

that children with the early-onset eczema before age 2 are not only associated with higher prevalence of sensitization to milk but also increased risk of allergic rhinitis and asthma development during childhood, suggesting that eczema onset in infancy related to milk sensitization may precede the subsequent development of allergic airway diseases in early childhood.

Eczema is a common allergic reaction and food allergen sensitization plays a considerable role. The sensitization to food allergens occurs early in life; however, the prevalence of food sensitization decreases, accompanied with increased inhalant allergen sensitization at older age.^{4,13,14} Egg white and milk are the two most common food allergies in infant and young Asian children.^{10,15} In this study, children with eczema featured high prevalence of sensitization to food, especially to milk, supporting the strong association between eczema and food sensitization. Furthermore, the significantly high prevalence of milk sensitization found in children with early-onset eczema indicates that early life sensitization to milk may precede the development of infantile eczema.

IgE is a type of antibody representing an allergic reaction in response to the allergens.¹⁶ The increased IgE levels may contribute to a severe allergic response and the risk of developing atopic diseases.¹⁷ However, the total serum IgE levels could be induced by multiple allergen sensitizations with an addition effect,⁴ which may provide no particular explanation regarding the differences between the eczema and IgE levels observed in this study. By contrast, the eosinophils are multifunctional cells and critically involved in

Table 2 Association between different onsets of eczema and risk of developing allergic rhinitis and asthma at age 4.

Atopic diseases	n (%)	Eczema			
		Crude		Adjusted ^a	
		OR (95% CI)	p	OR (95% CI)	p
<i>Rhinitis (n = 68)</i>					
Never eczema	21 (23%)	1.00 (reference)		1.00 (reference)	
Early-onset	25 (45%)	3.68 (1.51–8.99)	0.004	3.71 (1.37–10.02)	0.010
Late-onset	22 (55%)	2.74 (1.14–6.57)	0.024	2.75 (1.07–7.07)	0.036
<i>Asthma (n = 30)</i>					
Never eczema	9 (10%)	1.00 (reference)		1.00 (Reference:)	
Early-onset	12 (22%)	4.12 (1.37–12.38)	0.012	3.80 (1.12–12.85)	0.032
Late-onset	9 (23%)	2.62 (0.85–8.04)	0.093	2.98 (0.80–11.02)	0.102

^a Adjusted for maternal age at delivery, gestational age, maternal atopy, parental smoking, any older siblings, household income, and different breastfeeding patterns. All *P*-values <0.05, which is in bold, are significant. CI, confidence interval; OR, odds ratio.

the initiation of Th2 immunity for various skin diseases and systemic allergic disorders.¹⁸ In this study, the elevated AEC was significantly associated with eczema at age of 1.5 years old, the age at which the highest prevalence of milk sensitization was observed, suggesting that increased eosinophilia activation producing a skewed Th2 immune response to milk sensitization may increase the susceptibility to allergies, especially eczema.^{19–21}

Atopic march is a well-known concept that demonstrates the progression of atopic diseases.^{22,23} In this study, eczema was significantly associated with the occurrence of allergic rhinitis and asthma during early childhood, consistent with the findings of previous studies indicating that eczema is profoundly recognized as a precursor of later developing atopic diseases.^{24–26} Most importantly, the children with early-onset eczema relating to milk sensitization presented higher risk of subsequent allergic diseases, supporting a recent meta-analysis study reporting that food sensitization during the first 2 years of life can identify children at high risk of allergic disease including eczema, asthma and allergic rhinitis.²⁷

Food allergens are relevant to childhood eczema, and the clinical symptoms decline with decreased food sensitization.²⁸ The sensitization to food occurs early in life; however, the sensitization to inhalant allergens occurs later in life and is more specific to allergic rhinitis and asthma development in early childhood.⁴ In this study, the children with late-onset eczema showed no association with food sensitization. However, these children were significantly associated with the development of allergic rhinitis relating to inhalant sensitization. These findings indicate that a late-onset eczema may be an allergic symptom commonly associated with allergic airway diseases later in life rather than specifically by food sensitization.

The major limitation of this study is the questionnaire-based diagnosis of eczema which may feature an over-identification of the diagnostic prevalence. However, the diagnosis of atopic diseases was also evaluated at the clinic during follow-up period, minimizing the rates of over-diagnosis allergy. Most importantly, the strength of the current study is its long-term follow-up with regular interval at clinic, allowing for the causal inferences of eczema regarding variable relations including sequential

measurement of total serum and allergen-specific IgE levels, and AEC.

In conclusion, in the early childhood, eczema appears to have increased the AEC, with higher prevalence of sensitization to milk, especially in children with early-onset eczema. Although both the early- and late-onset eczema are associated with higher prevalence of atopic diseases, early-onset eczema is significantly related to the increased risk of developing allergic airway diseases later in life. These findings suggest that early-onset eczema may not only be an allergic symptom associated with food sensitization but also precede the development of allergic rhinitis and asthma in early childhood.

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Conflicts of interest

All the authors declare no conflicts of interest in relation to the present study.

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