ORIGINAL ARTICLE

Variations in risk of asthma and seasonal allergies between early- and late-onset pediatric atopic dermatitis: A cohort study

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Background: Atopic dermatitis is associated with other allergic conditions, but variations in this "atopic march" are poorly understood.

Objective: To determine the impact of the age of atopic dermatitis onset on the risk for asthma and seasonal allergies.

Methods: A cohort study was performed using the Pediatric Eczema Elective Registry, which is an observational cohort of subjects with pediatric onset atopic dermatitis.

Results: In total, 3966 children were included, and 73% reported atopic dermatitis onset before age 2 years. At baseline, subjects with atopic dermatitis onset at ages 3 to 7 or 8 to 17 years had significantly lower rates of seasonal allergies and asthma than those with onset before age 2. During follow-up, the adjusted relative risks for incident seasonal allergies were 0.82 (95% confidence interval, 0.72-0.91) and 0.64 (95% CI confidence interval, 0.47-0.83) in the 3- to 7- and 8- to 17-years-old at onset groups compared with the age 2 years or younger at onset group. The adjusted risk for incident asthma was not significantly different between the older onset groups and the earliest onset group.

Limitations: Misclassification bias may arise from using self-reported onset age data.

Conclusions: The timing of atopic dermatitis onset may explain part of the variation in the atopic march. These findings may improve future risk stratification of patients for treatment. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2017.06.013.)

Key words: allergic rhinitis; asthma; atopic dermatitis; atopic march; eczema; epidemiology; hay fever; seasonal allergies.

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Atopic dermatitis (AD) is a chronic skin disease that affects 15% to 30% of children and accounts for nearly $3.8 billion in direct spending in the United States annually.[1-3] It is associated with the development of other forms of allergy, and this so-called atopic march is characterized by the progression from AD initially to seasonal allergies and asthma subsequently.[4] The defective barrier of AD-affected skin is thought to act as a site of primary sensitization, which then allows for allergic sensitization in the airways. Although an estimated 30% to 60% of patients with AD develop asthma and/or seasonal allergies,[5] not all individuals with AD complete the atopic march. This variation in the atopic march is not well characterized, and methods to risk-stratify patients are needed.

CAPSULE SUMMARY

- Patients with atopic dermatitis follow the "atopic march" to varying degrees.
- Early-onset atopic dermatitis before the age of 2 years is associated with a greater risk for seasonal allergies and asthma in children with atopic dermatitis.
- The age of disease onset may help to identify clinically meaningful subgroups of patients with atopic dermatitis.

One potential explanation for the varying risk for comorbid atopic conditions among patients with AD could be differences in the timing of AD onset. Genetic factors that predispose to earlier-onset AD may drive shared predispositions to other atopic conditions.[6,7] As repeated episodes of allergen exposure are associated with allergic sensitization in the airways, the likelihood of asthma and seasonal allergies may be higher with earlier-onset AD.[4] Although AD most commonly begins in infancy, it may not begin until after age 7 in up to one-third of patients.[8,9] A distinction between early-onset and late-onset AD has been previously made,[7,10-13] but its influence on the development of other atopy remains unclear. Prior studies have suggested a greater risk for asthma and seasonal allergies in children with AD onset in the first 2 years of life.[10-12,14] However, older ages of AD onset have not been adequately examined, and the duration of follow-up in prior studies has been relatively short. By understanding the relationship between age of AD onset and associated atopy, we may better risk-stratify patients and identify clinically meaningful subgroups of patients with AD. Thus, we performed a study to examine the impact of age of AD onset on the risk for seasonal allergies and asthma among children with AD.

MATERIALS AND METHODS

Study population

We conducted a cohort study using the Pediatric Eczema Elective Registry (PEER), an ongoing observational cohort of persons with pediatric-onset AD in the United States. PEER was initiated in 2004 to assess potential safety concerns of pimecrolimus, a topical calcineurin inhibitor commonly used to treat AD.[15] To date, PEER has already enrolled more than 7700 individuals, with a median follow-up duration of 7.5 years.

Enrollment criteria for PEER have been described in detail previously.[16-19] Briefly, all subjects were 2 to 17 years old at the time of registry enrollment and had a clinical diagnosis of AD confirmed by their physician. Enrolling physicians included dermatologists, pediatricians, allergists, and primary care physicians from across the United States. All subjects had used topical pimecrolimus for at least 42 days of the 180-day period preceding enrollment into PEER; however, they were not required to continue pimecrolimus use after enrollment, and many did not.[19] Exclusion criteria for PEER included lymphoproliferative disease, systemic or skin malignancy, or use of systemic immunosuppressants. In this study, we included only subjects with at least 3 years of follow-up because allergic outcomes were assessed every 3 years.

Informed consent or assent was obtained from all participants or their caregivers at the time of enrollment into PEER. Our study protocol was granted exemption by the institutional review board at the University of Pennsylvania.

Exposures and outcomes

The exposure of interest was the age of AD onset, which was directly reported by the subject or caregiver on a questionnaire administered at the time of registry enrollment. We categorized age of AD onset as 2 years or younger, 3 to 7 years, and 8 to 17 years, which are respectively referred to in this article as early-, mid-, and late-onset AD. AD onset before age 2 years was considered early-onset disease, as this is the most common definition used.[11-13,20,21] Although there is no uniform definition for late-onset AD, we defined it to be that starting after age 8, as 1 recent study found this age to best differentiate between patients with and without filaggrin mutations, which are a known genetic risk factor for AD, suggesting that this age cutoff may separate different subgroups of patients with AD.[6]

Abbreviations used:

AD: atopic dermatitis
CI: confidence interval
PEER: Pediatric Eczema Elective Registry
RR: relative risk

Observation time began when subjects enrolled into PEER. The baseline presence of asthma and seasonal allergies was assessed via the enrollment questionnaire, which asked subjects whether they had any of these conditions in the past or at present. During follow-up, subjects were mailed questionnaires every 3 years to assess for the development of asthma or seasonal allergies. Questions on asthma and seasonal allergies were adopted from the International Study of Asthma and Allergies in Childhood study.[22] The primary outcome was incident patient/caregiver-reported asthma and seasonal allergies in subjects without these conditions at baseline. As a secondary outcome, the baseline prevalence of asthma and seasonal allergies were compared across the 3 onset age groups by using a cross-sectional design. The enrollment questionnaire also assessed demographic characteristics and other covariates, including sex, race and ethnicity, age at registry enrollment, household income, personal history of allergies, family history of atopic disorders, and baseline AD symptoms.

Analysis

We examined the distribution of covariates among the 3 onset age groups by using the chi-square test for categorical variables and Kruskal-Wallis test for continuous data. A nonparametric test for trend was performed where appropriate. We compared the risk for prevalent and incident asthma and seasonal allergies among the 3 exposure groups by using regression analysis. Because seasonal allergies and asthma are common outcomes, odds ratios obtained from logistic regression would overestimate the actual relative risks (RRs). Thus, we used an accepted statistical method to convert odds ratios to RR estimates.[23] Logistic regression models were adjusted for covariates determined a priori, including sex, race/ethnicity, age at enrollment, and follow-up duration. As outcomes were assessed only every 3 years, we performed logistic regression rather than Cox regression. Baseline AD severity was also examined but was excluded from the final multivariable models as it may be a potential mediator in the biologic pathway linking AD to other atopic disorders. All statistical analyses were performed using Stata software (version 14.1, StataCorp, College Station, TX). The statistical significance level was set at $\alpha = 0.05$. All hypothesis tests were 2 sided.

RESULTS

In PEER, 3966 individuals had at least 3 years of follow-up and were included in the study. Of those individuals, 2913 developed AD before age 2, 725 developed AD at age 3 to 7, and 328 developed AD after age 8 (Table I). Forty-seven percent of the subjects were male. The study population consisted of 39.4% white, 46.3% black, and 7.7% Hispanic individuals. The median age at enrollment was 6.4 years (interquartile range, 4.0-10.2), and older enrollment ages were observed with older ages of AD onset. The duration of AD at enrollment was longer for subjects with earlier-onset AD (Table I). However, the median duration of follow-up was approximately 8 years in all 3 groups. At the time of PEER enrollment, 2908 subjects(73.3%) already had seasonal allergies and 1965 (49.5%) already had asthma, with the early-onset group having the greatest proportions (Table I).

At the time of registry enrollment, the prevalence values of seasonal allergies were 74.6%, 69.9%, and 70.1% in the early-, mid-, and late-onset groups, respectively (Table II). Relative to the early-onset group, the unadjusted RRs for prevalent seasonal allergies were 0.96 (95% confidence interval [CI], 0.93-0.99) and 0.92 (95% CI, 0.85-0.97) among the mid- and late-onset groups, respectively. After multivariable adjustment for sex, race, and age at registry enrollment, the RRs for prevalent seasonal allergies were 0.91 (95% CI, 0.88-0.95) and 0.82 (95% CI, 0.74-0.89) in the mid- and late-onset groups, respectively. Among the 1054 subjects who did not have seasonal allergies at baseline, the cumulative incidence values of new-onset seasonal allergies during follow-up were 56.1%, 46.8%, and 30.6% for the early-, mid-, and late-onset groups, respectively (Table II). The risk for incident (ie, new onset after PEER enrollment) seasonal allergies significantly decreased with increasing age category of AD onset, with adjusted RRs of 0.82 (95% CI, 0.72-0.91) and 0.64 (95% CI, 0.47-0.83) among the mid- and late-onset groups, respectively, compared with the early-onset group (Table II).

Baseline prevalence of asthma was highest among the early-onset group (51.5%, 44.7%, and 43.0% in the early-, mid-, and late-onset groups, respectively) (Table III). The adjusted RR for prevalent asthma was significantly lower in the mid- and late-onset groups (RR, 0.85, 95% CI 0.80-0.91 and RR, 0.71, 95% CI 0.61-0.82, respectively) than in the early-onset group

Table I. Baseline characteristics of subjects (N = 3966)

Characteristic	Age of AD onset			*P* value*
	Age ≤2 y (n = 2913)	Age 3-7 y (n = 725)	Age 8-17 y (n = 328)	
Male sex	1387 (47.61%)	338 (46.62%)	134 (40.85%)	.07
Race/ethnicity				
White (non-Hispanic)	1183 (40.61%)	254 (35.03%)	124 (37.80%)	
Hispanic	211 (7.24%)	73 (10.07%)	23 (7.01%)	
Black/African American (non-Hispanic)	1324 (45.45%)	342 (47.17%)	170 (51.83%)	.01
Asian or Pacific Islander	94 (3.23%)	31 (4.28%)	4 (1.22%)	
American Indian/Alaskan native	18 (0.62%)	4 (0.55%)	2 (0.61%)	
Multiracial	83 (2.85%)	21 (2.90%)	5 (1.52%)	
Annual household income				
$0-$24,999	1022 (35.10%)	267 (36.88%)	127 (38.72%)	.03
$25,000-$49,999	477 (16.38%)	111 (15.33%)	51 (15.55%)	
$50,000-$74,999	306 (10.51%)	66 (9.12%)	27 (8.23%)	
$75,000-$99,999	202 (6.94%)	35 (4.83%)	18 (5.49%)	
≥$100,000	219 (7.52%)	39 (5.39%)	17 (5.18%)	
Prefer not to answer	686 (23.56%)	206 (28.45%)	88 (26.83%)	
Age at enrollment, y, median (IQR)	5.2 (3.4-8.5)	8.3 (6.5-10.9)	13.1 (11.3-15.1)	<.001
AD disease duration at enrollment, y, median (IQR)	4.5 (2.6-7.7)	3.7 (1.9-6.4)	2.1 (1.3-3.7)	<.001
Duration of follow-up, y, median (IQR)	8.4 (5.9-9.8)	8.2 (5.4-9.9)	8.4 (5.5-9.9)	.03
AD disease control at enrollment				
Complete	129 (4.43%)	31 (4.29%)	26 (7.93%)	<.001†
Good	1327 (45.59%)	393 (54.36%)	161 (49.09%)	
Limited	1158 (39.78%)	230 (31.81%)	113 (34.45%)	
Uncontrolled	297 (10.20%)	69 (9.54%)	28 (8.54%)	
History of asthma	1500 (51.53%)	324 (44.69%)	141 (42.99%)	<.001†
History of seasonal allergies	2171 (74.63%)	507 (69.93%)	230 (70.12%)	.01†
Family history of				
Eczema	1697 (58.26%)	386 (53.24%)	153 (46.65%)	<.001†
Asthma	1268 (43.53%)	300 (41.38%)	148 (45.12%)	.45
Seasonal allergies	1600 (54.93%)	371 (51.17%)	188 (57.32%)	.11

AD, Atopic dermatitis; *IQR*, interquartile range.
*Chi-square or Kruskal-Wallis test.
†Nonparametric test for trend.

Table II. Prevalence of seasonal allergies at enrollment and incidence of new-onset seasonal allergies during follow-up

Prevalence and incidence	Age of AD onset		
	Age ≤2 y	Age 3-7 y	Age 8-17 y
Prevalence of seasonal allergies at baseline (N = 3966)			
Prevalence (%)	2171/2909 (74.6%)	507/725 (69.9%)	230/328 (70.1%)
RR (95% CI), unadjusted	1 (ref)	0.96 (0.93-0.99)	0.92 (0.85-0.97)
RR (95% CI), adjusted*	1 (ref)	0.91 (0.88-0.95)	0.82 (0.74-0.89)
Incidence of seasonal allergies during follow-up (N = 1054)			
Cumulative incidence (%)	414/738 (56.1%)	102/218 (46.8%)	30/98 (30.6%)
RR (95% CI), unadjusted	1 (ref)	0.79 (0.71-0.87)	0.59 (0.45-0.75)
RR (95% CI), adjusted†	1 (ref)	0.82 (0.72-0.91)	0.64 (0.47-0.83)

AD, Atopic dermatitis; *CI*, confidence interval; *ref*, reference; *RR*, relative risk.
*Adjusted for sex, race (white, black, or other), and age at registry enrollment.
†Adjusted for duration of follow-up.

(Table III). Among the 1999 subjects without asthma at baseline, the cumulative incidence of new-onset asthma ranged from 29.9% in the late-onset group to 39.2% in the early-onset group (Table III). However, after adjustment for participant sex, race, age at enrollment, and duration of follow-up, the risks of incident asthma in the older-onset age groups were not significantly different from those in the

Table III. Prevalence of asthma at enrollment and incidence of new-onset asthma during follow-up

	Age of AD onset		
Prevalence and incidence	**Age ≤2 y**	**Age 3-7 y**	**Age 8-17 y**
Prevalence of asthma at baseline (N = 3966)			
Prevalence (%)	1500/2911 (51.5%)	324/725 (44.7%)	141/328 (43.0%)
RR (95% CI), unadjusted	1 (ref)	0.90 (0.85-0.95)	0.80 (0.71-0.89)
RR (95% CI), adjusted*	1 (ref)	0.85 (0.80-0.91)	0.71 (0.61-0.82)
Incidence of asthma during follow-up (N = 1999)			
Cumulative incidence (%)	553/1411 (39.2%)	128/401 (31.9%)	56/187 (29.9%)
RR (95% CI), unadjusted	1 (ref)	0.86 (0.79-0.94)	0.73 (0.60-0.89)
RR (95% CI), adjusted†	1 (ref)	0.96 (0.85-1.06)	0.92 (0.72-1.12)

AD, Atopic dermatitis; *CI*, confidence interval; *ref*, reference; *RR*, relative risk.
*Adjusted for sex, race (white, black, or other), and age at registry enrollment.
†Adjusted for duration of follow-up.

early-onset group (Table III). Additional adjustment for baseline AD disease control (rated as complete, good, limited, or uncontrolled) in the multivariable regression for both seasonal allergies and asthma did not alter the results (not shown).

DISCUSSION

In this study, we observed that early-onset AD is associated with a greater risk for seasonal allergies and asthma than later-onset AD is. Compared with children with AD onset before age 2, those with AD onset after age 8 had an 18% lower risk for prevalent seasonal allergies and 29% lower risk for prevalent asthma at the time of registry enrollment. Moreover, children without seasonal allergies at the time of or soon after AD onset were significantly less likely to develop such allergies in subsequent years (ie, incident allergies in our study) if their AD began after age 2. Children with late-onset AD had a 36% lower risk for incident seasonal allergies compared with children with early-onset AD. In contrast, we did not observe a statistically significant difference in the risk for incident asthma between the early- and late-onset groups. One potential explanation for this finding could be that if asthma were to develop, it would tend to occur very soon after AD onset and consequently lead to similar rates of incident AD across the different onset age groups during the later years of follow-up in our study. It may also be possible that age of AD onset affects asthma differently than it affects seasonal allergies.

Previous examinations of age of AD onset and other atopic conditions have been mixed. In repeated cross-sectional studies of 5- to 7-year-old German children, Mohrenschlager et al observed that early-onset AD before age 2 was associated with 6-fold increased odds of asthma by age 5-7 whereas late-onset AD was associated with 2-fold increased odds.[11] However, the odds of hay fever were similar for those with early- and late-onset AD. In another study, AD onset within the first 2 years of life was associated with an increased risk for asthma by age 7 in boys only.[14] In a cohort of children at high risk for atopy, Carlsten et al observed that children with early-onset AD had significantly greater odds of asthma by age 7 whereas only those with persistent and early-onset AD had significantly greater odds of allergic rhinitis by age 7.[12]

Our study is 1 of the few that have been designed primarily to examine the impact of age of AD onset on the risk for subsequent atopy. Unlike the authors of previous studies, we performed multivariable regression to adjust for potential confounders and estimated actual RRs, which are more appropriate than odds ratios for this study design and outcome. Furthermore, our study examined a larger number of patients with AD across a broader range of ages. Whereas prior studies have focused mostly on the development of other atopy before age 7, our study followed individuals into adolescence and early adulthood.

The finding that the risk of patients with AD for other atopic disorders varies by the timing of onset of their AD has several potential implications. First, the age of AD onset may be useful for disease prognostication and identification of clinically meaningful subgroups of patients with AD. Second, our results may improve the risk stratification of patients with AD for future treatment and prevention strategies targeting the atopic march, such as the biologic medications that have been recently approved or under development.[5] Our results may also inform the efficient design of future trials of such interventions. Third, early- and late-onset AD may differ in other clinically important ways beyond the atopic march, which is an area that warrants further study. Finally, although asthma and seasonal allergies risk vary by the age of AD onset, approximately 30% of

patients with late-onset AD still develop these disorders, underscoring the importance of screening all patients with AD for atopic comorbidities and counseling them on their future risk.

As with all studies, our study is not without potential limitations. First, misclassification bias and limitations in recall are possible with respect to self-reported data on age of AD onset. However, because we used 3 broad age categories rather than more granular data, the impact of this potential bias was minimized. There may also have been variation in the diagnosis of AD across different enrolling physicians in PEER. As with many observational cohorts of patients with AD, the Hanifin and Rajka criteria were not specifically used. However, because PEER is a population-level study, using a physician-based clinical diagnosis of AD is more generalizable and reflects the overall population of children with AD seeking treatment in the United States. Second, it is possible that individuals who enroll in PEER may be more likely to report concomitant illnesses, thereby leading to an overestimation of asthma and seasonal allergy rates. However, the rates of atopy observed in our study are similar to what has been previously reported in the literature.[5] Moreover, subjects in PEER were unaware of our study hypothesis, and we would not expect systematic bias in their reporting of atopic comorbidities by their age of AD onset. Third, loss to follow-up may be a limitation; however, the repeated survey response rate in PEER exceeded 75% on average at each time point.[17] Fourth, because PEER is not an inception cohort, subjects entered our cohort at different times in their AD disease course. However, if the null hypothesis that rates of asthma and seasonal allergy are similar across different ages of AD onset were true, then we would expect a higher incidence of other atopy in the older-onset groups because those participants were generally earlier in their AD disease course at PEER enrollment than participants with early-onset AD.

Finally, it is possible that our findings may not generalize to all patients with pediatric-onset AD. Because pimecrolimus is approved to treat mild to moderate AD and any individuals receiving systemic immunosuppressants were excluded from PEER, our results may be less generalizable to patients with severe AD. It is also possible that fewer subjects with later-onset AD were enrolled in PEER if they were less likely to be prescribed pimecrolimus, which may also limit generalizability. We also do not know how the heterogeneity and timing of treatments used for AD may modulate the risk for other atopy. An interaction may be possible between AD age of onset and pimecrolimus use on atopic outcomes; however, this potential interaction cannot be directly assessed as PEER lacks data on subjects without any pimecrolimus use. Nevertheless, topical calcineurin inhibitors are a common therapy approved for use across the full age range of eligible PEER subjects. Furthermore, subjects in PEER were not required to continue pimecrolimus use after enrollment into PEER, and many indeed did not.[19] Finally, PEER is 1 of the largest cohorts of patients with AD in the United States, and it provides a racially, economically, and geographically diverse study population.

In conclusion, our results suggest that the age of AD onset may explain part of the variation in the atopic march among children with AD. Future studies with longer follow-up and additional studies of adult-onset AD will help to confirm and extend our findings. Further characterization of early-onset and late-onset AD with respect to genetic risk factors and other outcomes, such as AD disease severity or response to therapy, will also be needed.

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