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]