Predicting the atopic march: Results from the Canadian Healthy Infant Longitudinal Development Study

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Background: The atopic march describes the progression from atopic dermatitis during infancy to asthma and allergic rhinitis in later childhood. In a Canadian birth cohort we investigated whether concomitant allergic sensitization enhances subsequent development of these allergic diseases at age 3 years.

Methods: Children completed skin prick testing at age 1 year. Children were considered sensitized if they produced a wheal 2 mm or larger than that elicited by the negative control to any of 10 inhalant or food allergens. Children were also assessed for atopic dermatitis by using the diagnostic criteria of the UK Working Party. At age 3 years, children were assessed for asthma, allergic rhinitis, food allergy, and atopic dermatitis. Data from 2311 children were available.

Results: Atopic dermatitis without allergic sensitization was not associated with an increased risk of asthma at age 3 years after adjusting for common confounders (relative risk [RR], 0.46; 95% CI, 0.11-1.93). Conversely, atopic dermatitis with allergic sensitization increased the risk of asthma more than 7-fold (RR, 7.04; 95% CI, 4.13-11.99). Atopic dermatitis and allergic sensitization had significant interactions on both the additive (relative excess risk due to interaction, 5.06; 95% CI, 1.33-11.04) and multiplicative (ratio of RRs, 5.80; 95% CI, 1.20-27.83) scales in association with asthma risk. There was also a positive additive interaction between atopic dermatitis and allergic sensitization in their effects on food allergy risk (relative excess risk due to interaction, 15.11; 95% CI, 4.19-35.36).

Conclusions: Atopic dermatitis without concomitant allergic sensitization was not associated with an increased risk of asthma. In combination, atopic dermatitis and allergic sensitization had strong interactive effects on both asthma and food allergy risk at age 3 years. (J Allergy Clin Immunol 2017;■■■:■■■-■■■.)

Key words: *Atopic march, asthma, allergic rhinitis, food allergy, atopic dermatitis, birth cohort, additive interaction, multiplicative interaction*

Many children have pruritic, chronic inflammatory skin disorders during the first year of life, variably called atopic dermatitis or eczema, affecting sleep and quality of life.[1,2] An estimated 10% to 20% of children worldwide have atopic dermatitis.[3] Interestingly, studies show that approximately two thirds of children given a diagnosis of classical atopic dermatitis are, in fact, not sensitized to allergens.[4] As a result, *atopic dermatitis* is a commonly used misnomer, prompting the World Allergy Organization to recommend in 2003 that the terms *atopic dermatitis* and *atopic eczema* be applied exclusively to atopic patients.[5]

The atopic march refers to the natural history of atopic manifestations, with a typical progression from atopic dermatitis to asthma and allergic rhinitis.[6] Several studies hypothesize a causal pathway,[6-11] including documentation of atopic comorbidities during a clinical trial of atopic dermatitis treatment[10] and a large retrospective study of atopic comorbidities based on health care provider diagnostic data.[11] Other studies suggest that the atopic march might oversimplify the natural history of childhood atopy.[12,13]

The connection between atopic dermatitis and asthma might be skin barrier dysfunction, specifically loss-of-function variants of the gene encoding filaggrin (*FLG*), a skin matrix protein that promotes aggregation of keratin filaments.[14] In the German Multicenter Allergy Study birth cohort *FLG* variants were highly

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Abbreviations used
aRR: Adjusted relative risk
CHILD: Canadian Healthy Infant Longitudinal Development
FLG: Filaggrin
RERI: Relative excess risk due to interaction
RR: Relative risk

predictive of asthma in children with eczema and sensitization to food allergens.[15] In the Isle of Wight birth cohort, allergic sensitization and eczema status were found to be independent effect modifiers of the relationship between *FLG* variants and asthma but not rhinitis.[16]

Because *FLG* genotyping is not typically available in clinical management,[9] alternative prognostic approaches for children with atopic dermatitis are needed. In particular, there has been a call for well-conducted longitudinal studies that compare differences in prognosis between sensitized and nonsensitized children.[4] This is especially important considering the global epidemic of asthma, allergy, and allergic rhinitis.[17] The Canadian Healthy Infant Longitudinal Development (CHILD) study[18] is a multicenter prospective birth cohort established to determine the root causes of allergic diseases in children. Here we investigated whether allergic sensitization enhances associations between atopic dermatitis in infancy with subsequent allergic diseases, including asthma, allergic rhinitis, food allergy, and persistent atopic dermatitis.

METHODS

Study design and cohort

The CHILD study is a multicenter longitudinal cohort of 3495 Canadian infants recruited during pregnancy and followed from birth to age 5 years. Child health questionnaires and clinical assessments of allergic diseases were conducted at regular intervals, including 1 and 3 years of age. The current analysis involves 2311 children who had complete data for clinical assessment at age 1 and 3 years, and all required adjustment variables.

Assessment of allergic sensitization

At age 1 year, children were administered epicutaneous skin tests to a battery of 6 inhalant (*Alternaria alternata*, cat hair, dog epithelium, house dust mites [*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*], and German cockroach) and 4 food (cow's milk, egg white, peanut, and soybean) allergens. As in our previous epidemiologic studies,[19-24] children were considered sensitized if they produced a wheal 2 mm or larger than that elicited by the negative control (glycerin) to at least 1 of the allergens. In cases in which skin tests were refused, some parents provided the results of external tests performed by other physicians, which were used to determine atopic status.

Assessment of allergic diseases

At the clinical assessment at age 1 year, the CHILD study physicians (A.B.B., P.J.M., P.S., and S.E.T.; all experienced pediatricians specializing in allergy and asthma) or other highly trained health care professional under their direction answered the question "Does this child meet the criteria for diagnosis of atopic dermatitis?" with the options "yes" or "no." These criteria were derived from the UK Working Party document,[25] namely an itchy skin condition with 1 or more of the following: a history of involvement of the skin creases of elbows, behind the knees, in front of the ankles, or around the neck; a history of general dry skin in the last year; or visible flexural eczema or eczema involving the cheeks/foreheads and outer limbs.

At the clinical assessment at age 3 years, the CHILD study physician or health care professional undertook a careful assessment of the clinical history during the past year and then responded to the following question: "In your opinion, does the child have any of the following: asthma, allergic rhinitis, food allergy, atopic dermatitis (Yes/Possible/No)?" Children were considered to have the outcome only if the response was definitively "yes." All diagnoses were reviewed by the study physician.

Covariate measures

Covariates considered in the study were child sex, study center, first-born status, ethnicity, household income, parental atopy based on skin prick testing, and parental self-reported history of allergic diseases (asthma, allergic rhinitis, food allergy, or atopic dermatitis). Parental atopy and disease history were considered positive if at least 1 of the parents had a positive test response (≥2-mm wheal to any allergen) or reported an allergic history. When data were missing for 1 parent and the other parent had a negative result, the child was considered not to have a parental history for atopy or allergic disease. Parental ethnicity was used to define child ethnicity, with a child considered white if at least 1 parent was white.

Statistical analysis

The relationship between atopic dermatitis and allergic sensitization at age 1 year with the outcomes of allergic disease at age 3 years was assessed by using multivariable modified Poisson regression.[26] Relative risks (RRs) and adjusted relative risks (aRRs) were calculated for both unadjusted and adjusted (for child's sex, study center, ethnicity, parental history of allergic diseases, and pet ownership) effects of atopic dermatitis and allergic sensitization at age 1 year. Interaction between atopic dermatitis and allergic sensitization was assessed in both the multiplicative and additive scales.[27,28] Multiplicative interaction was assessed by adding an interaction term to the adjusted and unadjusted model.

Relative excess risk due to interaction (RERI) was used to assess for additive interaction, in which an $RERI_{RR}$ value of greater than 0 indicates a positive additive interaction and an $RERI_{RR}$ value of less than 0 indicates a negative additive interaction. Calculation of 95% CIs was done by using the methods of variance estimates recovery.[29] The comparison group consisted of nonsensitized children without atopic dermatitis at age 1 year.

Two sensitivity analyses were undertaken. In the first analysis the definition of sensitization was changed from a wheal size of 2 mm or greater to a wheal size of 3 mm or greater, which is traditionally regarded as indicating clinically relevant sensitization. In the second analysis we excluded children with reported food allergy at age 3 months, 6 months, and/or 1 year to determine whether food allergy at age 3 years was simply a continuation of food allergy from early childhood.

All analyses were conducted with SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

Study population

At 1 year, among 2311 children eligible for this analysis, 317 (13.7%) were sensitized, with 252 (10.9%) sensitized to 1 or more food allergens and 95 (4.1%) sensitized to 1 or more inhalant allergens (Table I; for data on full cohort, see Table E1 in this article's Online Repository at www.jacionline.org). The most frequent food sensitization was to egg white (7.4%), followed by peanut (5.1%) and cow's milk (1.9%). At the 1-year clinic visit, 265 children were determined to have atopic dermatitis (11.5%). Considering allergic sensitization and atopic dermatitis, 221 (9.6%) children were sensitized but did not have atopic dermatitis, 169 (7.4%) had atopic dermatitis but were not sensitized, 96 (4.2%) had both, and 1825 (78.9%) had neither.

At the 3-year clinic visit, 81 (3.5%) of these 2311 children were considered to have definite asthma (53 received oral or inhaled