Predictive value of food sensitization and filaggrin mutations in children with eczema

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Background: It was reported that in infants with eczema and food sensitization, the presence of a filaggrin *(FLG)* null mutation predicts future asthma with a specificity and positive predictive value of 100%.

Objectives: We sought to evaluate the predictive value of food sensitization and food allergy, *FLG* haploinsufficiency, and their combination in infants with early-onset eczema for persistent eczema and childhood asthma.

Methods: The German Infant Nutritional Intervention (GINI) and Influence of Lifestyle-related Factors on the Immune System and the Development of Allergies in Childhood (LISA) birth cohorts, as well as a collection of 65 cases of early-onset eczema with and without food allergy were investigated.

Results: The risk for asthma was significantly increased by food sensitization (positive diagnostic likelihood ratios [PLRs] of 1.9 [95% CI, 1.1-3.4] in the GINI cohort and 5.5 [95% CI, 2.8-10.8] in the LISA cohort) and the presence of an *FLG* mutation (PLRs of 2.9 [95% CI, 1.2-6.6] in the GINI cohort and 2.8 [95% CI, 1.0-7.9] in the LISA cohort) with a rather high specificity (79.1% and 92.9% in the GINI cohort and 89.0% and 91.7% in the LISA cohort, respectively) but low sensitivity (40.0% and 39.3% in the GINI cohort and 31.6% and 23.5% in the LISA cohort, respectively). Likewise, the risk for persistent eczema was increased. In the clinical cases neither food allergy nor *FLG* mutations had a significant effect. The combination of both parameters did not improve prediction and reached positive predictive values of 52.3% (GINI cohort), 66.9% (LISA cohort), and 30.6% (clinical cases), assuming an asthma prevalence in children with early eczema of 30%.

Conclusion: Early food sensitization and the presence of an *FLG* mutation in infants with early eczema increase the risk for later asthma, but the combination of the 2 factors does not represent a clinically useful approach to reliably identify children at risk. (J Allergy Clin Immunol 2011;128:1235-41.)

Key words: *Eczema, atopic dermatitis, asthma, food sensitization, food allergy, filaggrin, prediction*

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Atopic dermatitis (eczema) is the most common inflammatory skin disease in childhood, with prevalence estimates of up to 20%.[1] Eczema is commonly associated with increased levels of total serum IgE antibodies and aberrant IgE-mediated responses to environmental agents. However, up to 50% of infants and children with eczema do not exhibit detectable specific IgE (sIgE) antibodies.[2-4] In those with early sensitization, the spectrum shifts from common food allergens (hen's egg, cow's milk, wheat, and soy) at age 1 year to aeroallergens at age 6 years.[5] Notably, subjects can have allergic sensitization to food allergens, as determined by skin prick testing or sIgE measurement, without having clinical symptoms on exposure to those foods.[6] Therefore diagnosis of IgE-mediated food allergy requires both the presence of sensitization and the development of specific signs and symptoms on exposure (ie, noneczematous immediate-type anaphylactic symptoms, eczematous delayed-type reactions, or combinations

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‡The members of the GINIplus and LISAplus study groups are shown in Appendix 1.

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Abbreviations used
DBPCFC: Double-blind, placebo-controlled food challenge
FLG: Filaggrin
GINI: German Infant Nutritional Intervention
LISA: Influence of Lifestyle-related Factors on the Immune System and the Development of Allergies in Childhood
MAS: Multicenter Allergy Study
NPV: Negative predictive value
PLR: Positive diagnostic likelihood ratio
PPV: Positive predictive value
RR: Relative risk
sIgE: Specific IgE

of both). Through not yet understood mechanisms, the time course of food allergy resolution in children varies by food and mostly occurs in early school-aged years.[7]

Eczema runs a chronic fluctuating course; about two thirds of children with early-onset eczema show spontaneous remission until early adolescence, whereas up to 20% have persistent eczema, and a further 17% show intermittent symptoms by age 7 years. Known risk factors for persisting eczema include severe disease, early allergic sensitization, and 2 or more first-degree relatives with atopic disease.[8]

Up to 50% of patients with childhood eczema go on to have asthma later in life.[5,9,10] However, it has been suggested that not eczema *per se* but rather early-onset eczema with specific allergic sensitization constitutes a risk for asthma.[8,11] In particular, early sensitization to hen's egg[12,13] and persistent (>1 year) sensitization to food allergens in children with early eczema[14] were reported to increase the risk for subsequent asthma and rhinitis. Findings from the German Multicenter Allergy Study (MAS) imply that allergic rhinitis until the age of 5 years is associated with wheezing between the ages of 5 and 13 years, yet this association is not attributable to eczema.[15]

To date, null mutations in the filaggrin gene *(FLG)* are the strongest and most widely replicated risk factor for eczema, particularly early-onset and persistent eczema with allergic sensitizations, and asthma in the context of eczema.[16-18] A very recent work indicated that FLG mutations might also be of relevance for peanut allergy independently from the presence of eczema.[19]

On the basis of observations made in the MAS cohort, it was further suggested that the combination of eczema, sensitization to food allergens, and *FLG* haploinsufficiency predicts childhood asthma with a specificity and a positive predictive value (PPV) of as much as 100%.[20] This is of great interest because it would mean that every infant with this combination will have asthma, that these infants could be identified early in life with the help of simple and rather easily measurable parameters, and that they could be subjected to early interventions and targeted prevention measures.[21] Overestimation of absolute risk, however, might lead to inadequate or inappropriate intervention in subjects whose asthma risk is actually lower than anticipated. Therefore we were interested to validate these observations and also to evaluate the usefulness of food sensitization and *FLG* mutation status for the prediction of the course of eczema. To this end, we investigated the German GINI and LISA birth cohorts, as well as a collection of carefully phenotyped children with eczema with or without confirmed food allergy.

METHODS

Study populations and phenotyping

German Infant Nutritional Intervention birth cohort. For the German Infant Nutritional Intervention (GINI) birth cohort, a total of 5991 full-term newborn infants were recruited from 2 regions of Germany (Munich and Wesel) between 1995 and 1998. The cohort is composed of intervention (n = 2252) and nonintervention (n = 3739) groups. For the current study, the intervention group was used. Briefly, the intervention study was a prospective, randomized double-blind trial designed primarily to examine the effect of different hydrolyzed infant formulas on the development of allergic diseases. Children with a positive family history of allergic disease were enrolled and invited to clinical examinations at 1, 4, 8, 12, and 36 months of age. For the first, second, and third years, diagnosis of eczema was made by using an algorithm of diagnostic criteria, as described previously.[22] sIgE levels against cow's milk, casein, α-lactalbumin, β-lactoglobulin, egg white, and soy allergen were measured at ages 12 and 36 months (Pharmacia and Upjohn Diagnostics AB, Uppsala, Sweden). Sensitization was defined as levels of 0.70 kU/L or greater (RAST class ≥2) against at least 1 of these allergens at 12 or 36 months. The whole birth cohort was followed up to now 10 years by self-administered questionnaires. At 6 and 10 years, a visit to the study center for clinical examination and blood sampling was offered. In participants of the 10-year follow-up visit, sIgE levels against aeroallergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, German cockroach, cat dander, mixed molds, timothy grass, mugwort, English plantain, ribwort, wall pellitory, and birch pollen) were determined. Sensitization was defined as an sIgE concentration of 0.35 kU/L or greater against at least 1 of the allergens.

Details of the design, recruitment, and follow-up of the study have been described previously.[22-25] The outcomes presented here are based on parental reports in the 10-year follow-up questionnaire. Asthma and eczema were defined as present if any physician had diagnosed asthma or eczema during the last 4 years, if the child was treated for asthma (eczema) in the last 12 months, or both. In the present analysis we included subjects with a clinical diagnosis of eczema in the first 3 years, known status of food sensitization, and available *FLG* genotypes who participated in the 10-year follow-up by questionnaire.

Influence of Lifestyle-related Factors on the Immune System and the Development of Allergies in Childhood birth cohort. For the Influence of Lifestyle-related Factors on the Immune System and the Development of Allergies in Childhood (LISA) birth cohort, 3097 newborns were initially recruited between 1997 and 1999 from 4 German cities: Munich, Leipzig, Wesel, and Bad Honnef. Data on the children's health and on lifestyle factors were collected by using repeated parent-completed questionnaires at regular time intervals during the first 2 years of life (6, 12, 18, and 24 months) and at 4, 6, and 10 years of age. Early eczema was defined if 1 positive answer was given to the following question: "Has a doctor diagnosed your child with allergic or atopic eczema in the past 6 months?"

Blood samples were drawn at 2, 6, and 10 years of age. At 2 years of age, total IgE and sIgE levels against a set of common food allergens (egg white, cow's milk, wheat, peanut, soybean, and codfish) were measured by using the CAP-RAST FEIA system (Pharmacia Diagnostics, Freiburg, Germany). Allergic sensitization against food allergens was defined as a specific serum IgE concentration of 0.7 kU/L or greater against at least 1 of the allergens. The design and objectives of this prospective birth cohort study were described in detail elsewhere.[26] Total IgE and sIgE levels against aeroallergens were measured at 10 years of age. The definition of outcome variables at age 10 years is identical to that of the GINI cohort.

Clinical case series. Of children with eczema aged 0 to 2 years who had been recruited in Munich for genetic studies between 2004 and 2006 (for details, see Weidinger et al[16]) and whose parents had given informed consent to be recontacted for follow-up, we randomly selected and reinvited 50 children with well-defined food allergy, as well as 50 children without any detectable sensitization and no history of adverse reactions to food. sIgE data from an enzyme immunoassay (CAP-FEIA; Pharmacia, Uppsala, Sweden) for a panel of food allergens (egg white, cow's milk, α-lactalbumin, β-lactoglobulin, peanut, soybean, wheat, codfish, and casein) and aeroallergens (mixed grass pollen, *D pteronyssinus*, *D farinae*, birch pollen, mugwort pollen, cat