Atopic sensitization in the first year of life

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Background: There is conflicting evidence on whether allergen-specific memory is primed prenatally, whether this priming affects persistent immunologic effects, and whether it is modulated by the first environmental exposures in infancy.
Objective: We sought to explore the course of atopic sensitization between birth and 12 months of age.
Methods: Specific IgE levels for 6 food and 13 common inhalant allergens were assessed in cord blood and 1-year blood samples in the Protection against Allergy–Study in Rural Environments (PASTURE) birth cohort including 793 children from rural regions of 5 European countries. Detailed information on children's health, nutrition, and farm-related exposures was gathered by using a pregnancy questionnaire, 2 questionnaires at 2 and 12 months of age, and a diary covering the time in between.
Results: Sensitization was more common at 12 months of age than at birth for almost all specificities. On an individual level, persistent sensitization to the same allergens was rare (1%), whereas transient (only at birth, 11%) and incident (only at 12 months, 34%) sensitization was seen in substantial proportions of children. Associations of transient sensitization with maternal sensitization differed with the allergen specificities, with the strongest associations for food allergens (odds ratio [OR], 10.6; 95% CI, 6.0-18.6) and the weakest associations for seasonal allergens (OR, 1.64; 95% CI, 0.94-2.86). Associations of maternal sensitization with incident sensitization were also seen. Incident sensitization was related to distinct prenatal and postnatal environmental exposures of mother and child, such as consumption of cereals for incident sensitization to seasonal allergens (OR, 0.66; 95% CI, 0.50-0.88).
Conclusion: IgE sensitization patterns change between birth and 12 months and are related to maternal and environmental influences. (J Allergy Clin Immunol 2013;131:781-8.)

Key words: *Atopic sensitization, early life, environmental exposures*

A central hallmark of an immune response to allergens is the detection of IgE antibodies. Hence it is crucial to study atopic sensitization by measuring specific IgE levels at various stages of development, including the prenatal period.

Currently, it is not known whether the immune system can mount a prenatal IgE response to specific allergens. Detection of allergen-specific IgE in cord blood is a subject of debate because contamination of cord blood by maternal IgE remains an open question.[1-4]

Furthermore, the effect of maternal exposure to allergens and other environmental stimuli on the fetal immune response has to be evaluated, and its persistence beyond the perinatal period remains to be determined. In the context of farm-related exposures, we have previously found an inverse association of maternal farm exposure during pregnancy and an IgE response to seasonal allergens in cord blood,[5] which has also been observed at school age.[6] However, the development of IgE production in the interval between birth and school age and its effect on disease manifestation remain unclear.

The aim of the present analysis of the Protection against Allergy–Study in Rural Environments (PASTURE) birth cohort is to characterize atopic sensitization within the first year of life. We focus on this time window because fundamental changes in allergen exposure take place during this period. First, direct exposure to inhalant allergens occurs with the first breaths and is followed by sequential introduction of different foods and their

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Abbreviations used
aOR: Adjusted odds ratio
PARSIFAL: Prevention of Allergy Risk factors for Sensitization
PASTURE: Protection against Allergy–Study in Rural Environments
OR: Odds ratio

allergens. We hypothesized that maternal and environmental factors influenced the development of atopic sensitization already in this early period of life.

In this analysis we classify sensitization patterns with respect to changes between birth and the age of 12 months. We distinguish between incident sensitization, persistent sensitization, and transient sensitization (Table I). Furthermore, we assess the relation between sensitization and environmental exposures, as determined by using a pregnancy questionnaire and weekly or monthly diaries during the first year of life.

METHODS

Study design and population

PASTURE has been set up to study the development of childhood asthma and allergies in a prospective birth cohort, including children from rural areas in 5 European countries: Austria, Finland, France, Germany, and Switzerland. The study design has been described earlier.[7] In 2002-2005, pregnant women were contacted in the third trimester of pregnancy. Women who lived on family-run livestock farms were assigned to the farm study group. For the reference study group, women from the same rural areas but not living on a farm were recruited. The study was approved by the ethics committees of the participating institutions, and written informed consent was obtained from the children's parents or guardians.

Specific IgE in serum samples

Specific IgE for 6 food and 13 common inhalant allergens was assessed in cord blood samples and at the age of 12 months in peripheral blood by using the semiquantitative Allergy Screen test panel for atopy (Mediwiss Analytic, Moers, Germany) in a central laboratory. This method has previously been validated against the *in vitro* IgE CAP system (Pharmacia, Freiburg, Germany) and the skin prick test, with a low intra-assay imprecision.[8] Cord blood and 12-month blood samples were not measured at 2 different time points but rather in the sequence they arrived at the central laboratory (see Fig E1, *A*, in this article's Online Repository at www.jacionline.org). Because some centers had started earlier with recruitment, they already had their 12-month specimens measured when other centers were just submitting their cord blood specimens. For each subject, a positive control was measured to standardize the biotin/streptavidin reaction. Food allergens included hen's egg, cow's milk, peanut, hazelnut, carrot, and wheat flour; inhalant allergens comprised *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, horse, and dog as perennial allergens and *Alternaria* species, mugwort, plantain, alder, birch pollen, hazel pollen, rye pollen, and a grass pollen mix as seasonal allergens. In addition, peripheral blood samples of the mothers were taken at birth (in Switzerland and Finland) or at a home visit when the child was 2 months old (Austria, France, and Germany) and were assessed for the same IgE specificities.

Diary and questionnaires

Questionnaires were based on items from the Asthma Multicenter Infants Cohort Study (AMICS),[9] the Allergy and Endotoxin (ALEX) study,[10] the Prevention of Allergy Risk Factors for Sensitization In Children Related to Farming and Anthroposophic Lifestyle (PARSIFAL) study,[11] and the American Thoracic Society questionnaire.[12]

Questionnaires were administered at the end of pregnancy and when the children were 2 and 12 months of age. The questions referred to the general health of the children's families, with a focus on respiratory and atopic diseases and maternal health during pregnancy. Additional detailed information on the children's health, nutrition, and farm-related exposures was gathered by using a diary covering the 9th to 52nd weeks of life. Questions about the children's health included occurrence and quantity of infections or symptoms (cough, wheeze, runny nose, fever, otitis, pneumonia, diarrhea, urinary tract infection, and rash). Farm-related exposures referred to the contact with animals and their feed and litter material. The children's diet was assessed with respect to the type of supplemental food and the time point of its regular introduction (ie, at least weekly consumption of the respective food). Furthermore, the parents were asked whether they bought the food in a shop or directly from a farm and whether they prepared the meals themselves or used convenience food.

Statistical analysis

Statistical analysis was performed with SAS 9.2 software (SAS Institute, Cary, NC). Specific IgE levels in children and mothers were dichotomized at the detection limit of 0.2 IU/mL to compare IgE levels in peripheral blood with the low IgE levels in cord blood. A higher cutoff of 0.35 IU/mL was also explored. In addition to specific IgE to the particular allergens, combinations of specific IgE were defined for IgE to seasonal, perennial, and food allergens. Combined variables were created to reflect the time course in atopic sensitization between birth and 12 months (Table I). *Never sensitized* was defined as the absence of detectable IgE to the same allergen specificity at birth and at 12 months. *Incident sensitization* was defined as detectable IgE at 12 months but not at birth. *Transient sensitization* was defined as detectable specific IgE at birth but not at 12 months. *Persistent sensitization* was defined as detectable specific IgE for the same allergen specificity at birth and at 12 months. When testing associations or concordances, the never sensitized category served as a reference category for all others.

Agreement between detectable IgE levels between birth and 12 months was assessed by using the McNemar test. Farm and reference children were compared for detectable IgE by using the Fisher exact test. Concordances between detectable IgE levels at birth and 12 months were calculated by using the Kendall τ partial on study center and study group.

The data provided by questionnaires and diaries were reduced by combination variables, reflecting quarterly or annual exposure and subsequent variable cluster analysis. Early exposure was defined by the time point of first contact to an exposure (food, day care, infections, or a farm-related exposure) and coded by using 5 categories (never or in the fourth, third, second, or first quarters). Infections were also assessed with respect to the frequency of episodes and the diversity of disease entities. The 152 variables representing environmental determinants and potential confounders were first tested for associations with incident sensitization in models only adjusted for farming and study center. The 31 variables with P values of less than .05 were subsequently entered in multiple logistic regression by using stepwise selection. In addition to the core model from the stepwise regression, an extended model was established, including potential standard confounders and variables on maternal IgE to the respective allergens. Because the study was based on previous knowledge and the variables were intercorrelated, corrections for multiple testing were not performed, which is well accepted in classical epidemiology.[13] Nevertheless, a conservative significance level of 1% was chosen for the stepwise regression models. In addition, a factor analysis based on the correlation matrix of all exposure variables was performed with varimax rotation, extracting 15 factors. Because exposure variables were continuous, categorical, or dichotomous, all variables were rescaled to a range of 0 to 1, and the Kendall τ value was used to calculate the correlation matrix. The respective factors were then entered into logistic regression models for incident sensitization to seasonal, perennial, and food allergens. These models were adjusted for center and maternal IgE level to the same allergen. The resulting P values were corrected for 15 tests.

Center homogeneity was assessed based on interaction terms in logistic regression models. Models for persistent sensitization could not be established because of its low frequency. The models for transient sensitization did not

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