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The association of maternal prenatal IgE and eczema in offspring is restricted to nonatopic mothers

William B. Hicks, MD[1], **Christian G. Nageotte, MD**[1], **Ganesa Wegienka, PhD**[2], **Suzanne Havstad, MA**[2], **Christine Cole Johnson, PhD**[2], **Dennis R. Ownby, MD**[3], and **Edward M. Zoratti, MD**[1]

[1]Division of Allergy and Clinical Immunology, Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, USA

[2]Department of Biostatistics and Research Epidemiology, Henry Ford Hospital, Detroit, MI, USA

[3]Division of Allergy and Clinical Immunology, Department of Pediatrics, Medical College of Georgia, Augusta, GA, USA

Abstract

The risk of developing eczema is thought to be influenced by both genetic and environmental factors. Prenatal factors including the intrauterine environment may influence risk. We examined the relationship of maternal total IgE obtained during pregnancy to the incidence of atopic dermatitis in their 2 year-old offspring. Subjects were participants in an unselected Detroit area birth cohort. Serum IgE was measured from 458 mothers in the third trimester of pregnancy along with prenatal family and environmental histories. Children were evaluated at approximately two years of age for current or past eczema by maternal questionnaire and physician examination. Among the 458 children, 20.3% (n=93) had a doctor confirmed diagnosis of eczema. Prenatal IgE was higher among women whose children developed AD versus women whose children did not. [Geometric means and 95% confidence intervals 52.7 IU/ml (40.9–68.0) versus 32.9 IU/ml (28.0–38.7), p= 0.010] The association was only seen in a subgroup of 181 women without allergic sensitization (specific IgE > 0.35 IU/ml) to a panel of 8 common allergens. Of the women without allergic sensitization, the mean serum IgE was 24.1 IU/ml (15.5–37.6) among those whose children had a diagnosis of eczema. The mean serum IgE was 11.2 IU/ml (9.2–13.6) among those whose children did not have a diagnosis of eczema (p-value 0.002). Maternal prenatal IgE level among women who are not sensitized to common allergens is associated with increased risk of eczema in offspring.

Keywords

Eczema; IgE; prenatal; maternal atopy; atopic dermatitis

Introduction

Eczema is associated with the subsequent development of allergic disorders, a phenomenon that has been described as the “allergic march” with atopic dermatitis being a potential harbinger of subsequent asthma and allergic rhinitis.[1, 2] The causes of eczema appear to be multifactorial with both genetic and environmental components[3] considered important in its etiology. The prenatal environment may influence the subsequent risk of eczema; A variety of prenatal[4] and perinatal[5] factors have been associated with increased risk. A limited

Reprint requests: Edward M. Zoratti, Henry Ford Health System, One Ford Place 4B, Detroit, MI 48202, ezoratt1@hfhs.org.

number of studies have previously assessed maternal prenatal IgE as a predictor of eczema.[6, 7] In order to assess a potential link between maternal IgE level during pregnancy and the risk of childhood eczema, we analyzed data obtained from a population-based birth cohort.

Methods

The Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) is an ongoing population based birth cohort study in southeastern Michigan. There were 1258 women [average=30.1 years (sd=5.1) range 21.0 to 43.9] residing in a predefined geographic area in and near Detroit Michigan, that were recruited from five Henry Ford obstetrics clinics during their pregnancy without consideration of their allergic disease history.

At the time of recruitment, September of 2003 through November 2007, pregnant women were interviewed to obtain their pregnancy, atopic dermatitis, asthma and allergy histories. The fathers' histories were obtained at this time from the mothers if known. Participant's race (self-reported using the US census categorization), education level and household smoking status were also queried.

Blood samples were obtained from the participants at the time of recruitment. Total IgE as well as specific IgE to common allergens were determined. Measurements were performed using Pharmacia UniCap system (Phadia, Portage, MI, USA) using the manufacturer's protocol, which provides an assay range of 2–1000 IU/ml of IgE. Samples with initial values >800 IU/ml were diluted ten-fold or more and reassayed to obtain precise values. Allergen-specific IgE levels were determined for 8 allergens including *Dermatophagoides farinae* (DerF), *Ambrosia artemisiifolia* (ragweed), *Alternaria alternatum*, dog, cat, *Phleum pratense* (Timothy grass), *Blatella germanica* (German Cockroach) and hen's egg. Maternal seroatopy was defined as having a specific IgE level of 0.35 IU/ml or greater to at least one of the specific allergens tested.

Children were evaluated by an allergist or pediatrician using history, physical examination and SCORAD (a system to quantify symptoms and signs of current atopic dermatitis).[1] The physician was then asked to record a response to the following question: "By your clinical evaluation do you believe that this child has or has had atopic dermatitis or eczema?" This evaluation was completed at a "2 year visit" (mean age of 2.2 years [sd=0.2] range 1.6 to 3.1). Other risk factor variables considered in the analyses included cord blood total IgE level and maternal history of atopic disorders as well as maternal race, the baby's sex, birth order, attendance at daycare in the first 6 months of life, maternal smoking and prenatal exposure to a dog or cat.

Due to skewness of the data, Wilcoxon rank sum tests were used to compare IgE measurements between those with and without a doctor diagnosis of eczema. Chi-square tests were used for binary variables. Logistic regression modeling was used to test for interaction effects and for multivariable analyses. IgE was used as a continuous variable in all analyses and log-transformed prior to inclusion in regression modeling.

Results

Of the women initially enrolled, 458 participated in a subsequent follow-up appointment when their offspring were 2–3 years old. Selected maternal characteristics included 53% African American ethnicity (with the majority of the remaining mothers being Caucasian); 56% exhibiting atopy (sensitized to one of 8 common aeroallergens); 19.4% reporting a

positive personal history of eczema; and 18.8% reporting a history of asthma. Of the 458 mothers, 93 (20.3%) had children classified as having current or prior eczema at the 2 year visit.

We found that prenatal IgE differed between mothers whose offspring had developed atopic dermatitis (geometric mean=52.7 IU/ml) versus those whose offspring did not (geometric mean=32.9 IU/ml, p=0.010). (Table 1) Women with seroatopy and those with a history of asthma or atopy were more likely to have children with eczema. Children with eczema were also more likely to have mothers of African American ethnicity (p= 0.015), with atopy (p-value 0.028) but were less likely to keep pets during pregnancy (p=0.005).

Of these factors, only maternal seroatopy was found to be a significant effect modifier of the relationship between maternal prenatal total IgE and eczema (interaction p value =0.010). Non-seroatopic mothers (n=152) whose offspring had eczema had higher prenatal IgE versus those whose offspring didn't develop eczema (geometric means 24.3 IU/ml vs. 11.7 IU/ml, p=0.01). In contrast, IgE levels in seroatopic mothers were similar when comparing those whose children developed eczema (73.9 IU/ml), versus those that did not (78.7 IU/ml, p = 0.57). No other factors modified or confounded the associations between maternal prenatal total IgE and the odds of eczema in the child.

A multivariate analysis of potential factors that were independently associated with eczema in offspring, stratified by maternal seroatopy, is presented in Table 2. Among 242 seroatopic mothers, the adjusted odds ratio of an association of eczema with maternal prenatal total IgE level was 0.89 (1 unit change in IgE 95% CI of 0.67–1.18, p=0.4), but among 181 non-seroatopic mothers, the adjusted odds ratio was 1.83 (1.21–2.77, p=0.004).

Discussion

Our results show that prenatal maternal IgE is associated with eczema in their preschool aged offspring. Interestingly, the association is restricted to non-atopic mothers. Furthermore, in this population, in addition to evidence of atopy, the relationship is independent of parental reports of symptomatic disorders indicative of possible allergic disease or disorders mimicking allergy including a history of asthma, eczema or allergy.

Few studies have closely examined maternal prenatal IgE levels and subsequent development of eczema in their offspring Liu et al.[6] reported a higher risk of eczema in 6 month old infants whose mothers' IgE levels were higher than 150kU/L (>80th percentile) among 545 families from a birth cohort in Kaohsiung Taiwan). The risk of eczema was 22% when maternal IgE was higher than this cutoff level versus 13% with lower IgE levels (OR 2.6; 95%CI 1.2–5.7) in a multivariate analysis including parental history of allergy and presence of atopy. Similarly, Kurzius-Spencer et al.[7] reported in the Tucson Infant Immune Study, an elevated risk of infantile eczema among mothers whose serum IgE level was in the highest tertile (>60.9 kU/L, OR 2.28 [1.2–4.4]. Taking an alternative analytic approach by assessing maternal IgE as a continuous variable, our data are consistent overall with these reports. However, the prior publications do not report a dependency of the association on maternal atopic status, whereas we found the association was entirely restricted to children from non-atopic mothers. Since stratum-specific analyses were not performed in previous reports, an association present only in a subgroup could have been masked. We believe this additional information may be important as it further underscores mechanisms whereby IgE may be modulating the risk of eczema in addition to its recognized role in mediating immediate hypersensitivity to common allergens.

The fact that maternal but not paternal IgE levels are associated with infantile eczema suggests either a differentially higher risk via transmission of maternal genetic factors, more

closely shared environmental exposures between mother and infant,or potentially, a mechanism involving exposure to IgE via the fetal-maternal interface.[6] Although there has been considerable debate as to whether maternal IgE can be transferred to the circulation of the developing fetus, there is evidence that maternal IgE gains access to the amniotic fluid with the potential of stimulating CD23 receptors in the infant gastrointestinal tract.[8] Alternatively, maternal prenatal IgE may be a marker of other environmental conditions present in the maternal-fetal unit that may favor the development of AD in the child. One could speculate that transfer of Th2-like cytokines could be reasonably implicated. However, in the Tucson Infant Immune Study, maternal mitogen-induced cytokine production, including IL4, IL5 and IL13, did not correlate with risk of eczema in their offspring.[7] Furthermore, it is unclear whether cytokines, are directly transferred from mother to the fetus.[9, 10]

A strength of our study is the design. We had a birth cohort study with a trained physician determining diagnosis of eczema at 2 years. Also, maternal prenatal IgE was evaluated as a continuous variable versus using an arbitrary cutoff as in previous studies. We also evaluated this association with respect to seroatopy determined in mothers. Limitations include the fact that we were unable to obtain paternal prenatal IgE measurements as was done by Liu et al.[6] Further, our study is an observational study and does not address the potential mechanisms underlying these associations.

In conclusion, maternal prenatal IgE level is associated with increased odds of eczema in their offspring but this effect is only apparent in non-atopic mothers. The mechanism by which maternal IgE influences the risk for eczema in their offspring requires further study.

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Table 1

Characteristics associated with the presence of Eczema in offspring

	Physician assessment positive for AD		
Characteristic	**Yes N=93**	**No N=365**	**p-value[1]**
Maternal pre-delivery total IgE [Geometric mean (95% CI)]	52.7 (40.9–68.0)	32.9 (28.0–38.7)	0.0102
Maternal atopy (specific IgE > 0.35 kU/L)			0.028
- Yes	62 (23.9%)	197 (76.1%)	
- No	31 (15.6%)	168 (84.4%)	
Cord blood total IgE	0.38 (0.27–0.53)	0.28 (0.24–0.33)	
[Geometric mean (95% CI)]	n=78	n=326	0.14[2]
Maternal history of doctor diagnosis of eczema			
- Yes	16 (18.2%)	72 (81.8%)	0.62
- No	75 (20.5%)	290 (70.5%)	
Maternal history of doctor diagnosis of asthma			0.052
- Yes	24 (27.9%)	62 (72.1%)	
- No	69 (18.5%)	303 (81.5%)	
Maternal report history of allergy (by questionnaire data)			0.19
- Yes	22 (25.9%)	63 (74.1%)	
- No	71 (19.4%)	294 (80.6%)	
Maternal Race			
- African American (AA)	60 (24.6%)	184 (75.4%)	0.015
- Not AA	33 (15.4%)	181 (84.6%)	
Baby sex			
- Male	55 (23.3%)	181 (76.7%)	0.10
- Female	38 (17.1%)	184 (82.9%)	
Maternal smoking			
- Yes	5 (12.5%)	35 (87.5%)	0.20
- No	88 (21.0%)	330 (79.0%)	
Had pet during pregnancy			
- Yes	26 (14.0%)	160 (86.0%)	0.005
- No	67 (24.6%)	205 (75.4%)	
First born			
- Yes	31 (18.6%)	136 (81.4%)	0.48
- No	62 (21.3%)	229 (78.7%)	

	Physician assessment positive for AD		
Characteristic	**Yes N=93**	**No N=365**	**p-value[1]**
Daycare			
- Yes	33 (22.6%)	113 (77.4%)	0.40
- No	60 (19.2%)	252 (80.8%)	

[1] all p-values from chi-square test unless noted otherwise;

[2] p-value from Wilcoxon rank sum test

Table 2

Multivariable model of potential factors associated with childhood eczema stratified by maternal atopic status

Sero-atopic mothers only (N=242)			
	Adjusted OR*	95% confidence interval	p-value
Log-transformed maternal IgE	0.89	0.67 – 1.18	0.40
Maternal history of asthma	1.95	1.05 – 3.64	0.036
Maternal history of allergy	0.78	0.38 – 1.61	0.51
Maternal history of eczema	1.03	0.45 – 2.33	0.94
Non-sero-atopic mothers (N=181)			
	Adjusted OR*	95% confidence interval	p-value
Log-transformed maternal IgE	1.83	1.21 – 2.77	0.004
Maternal history of asthma	0.92	0.27 – 3.12	0.90
Maternal history of allergy	0.37	0.11 – 1.27	0.12
Maternal history of eczema	0.20	0.02 – 2.23	0.19

* adjusted for all other variables on table as well as maternal race, sex of baby, and maternal smoking, first born status, daycare attendance and pet-keeping during pregnancy.