

Elevated cord blood IgE is associated with recurrent wheeze and atopy at 7 yrs in a high risk cohort

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There is considerable interest in identifying children at high risk for developing atopic diseases for primary prevention. This study evaluates risk factors for detectable cord blood IgE and assesses CB-IgE in predicting asthma and other IgE-mediated allergic diseases in children at high risk because of family history. Cord blood was obtained as part of a randomized controlled trial assessing the efficacy of an intervention program in the primary prevention of IgE-mediated allergic diseases. CB-IgE was measured and the degree to which this was associated with perinatal risk factors was assessed. The cohort was then evaluated for atopic disorders at 7 yrs of age to assess the predictive value of CB-IgE. Fifty-five (19.3%) of infants had detectable CB-IgE (≥ 0.5 kU/l). Maternal atopy and birth in winter months were risk factors associated with detectable CB-IgE. CB-IgE was found to be significantly associated with allergic sensitization (OR 2.22; 95% CI 1.11, 4.41) and recurrent wheeze at 7 yrs (OR 2.51, 95% CI 1.09, 5.76) but not with other outcomes. CB-IgE may be a useful measure for identifying children at high risk of atopic diseases for the purpose of primary prevention.

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The increasing prevalence of asthma and allergic diseases in many countries along with the increasing health care burden have led to considerable interest in primary prevention of these diseases through environmental controls (1). As measures for control of indoor allergens are often difficult and expensive, and generally require long-term implementation, it may be more efficient to apply them only to a high risk group. Cord blood serum IgE (CB-IgE) has been studied as a predictor of asthma and other IgE-mediated allergic diseases but the results are controversial. While some studies showed that it is a good predictor (2, 3), others failed to do so (4, 5). We have reported previously that infants from a birth cohort of children with a high risk for allergic disease, studied in a randomized

controlled trial for primary prevention of asthma and having high CB-IgE had a significantly increased risk of developing urticaria from food allergy at 12 months of age (6). This report evaluates the association of CB-IgE with various allergic diseases at the age of 7 yrs.

Materials and methods

Subjects

The cohort has been described in previous publications (6, 7). The study was carried out in two centers in Canada: Vancouver and Winnipeg. Briefly, mothers of high risk children, defined as having at least one first degree relative with asthma or two first degree relatives with

other IgE-mediated allergic diseases, were recruited during their last trimester of pregnancy. Families were randomly allocated to a multifaceted intervention ($n = 279$) or control (usual care, $n = 266$) group. The multifaceted intervention program was implemented before birth and continued through the first year of life. This included avoidance of house dust mites, pets and environmental tobacco smoke, encouragement of breastfeeding for at least 4 months and delayed introduction of other foods until 6 months of age. At 7 yrs of age, 380 (70%) returned for assessment.

Methods

Home visits were carried out before birth and at 1, 2 and 7 yrs after birth, when house dust samples were collected using a standard protocol, and a questionnaire regarding health and exposure was completed by the research nurse or technician (7). Allergen levels were determined using an ELISA assay with purified monoclonal antibodies against group 1 mite allergens, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (7).

Total CB-IgE levels were measured using paper radioimmunoabsorbent test commercially available kits (Pharmacia Diagnostics Inc, USA) and each sample was assayed in duplicate. The results of duplicates were highly correlated with each other ($r = 0.99$) as described previously (8).

At 2 and 7 yrs, allergy skin tests were performed by the epicutaneous method using a prick lanceter (Bayer Inc., Toronto, Canada) with the following allergens (Bayer Inc.): house dust mite (*D. pteronyssinus* and *D. farinae*), cat, and dog dander, *Alternaria alternata*, *Cladosporium herbarum*, peanut, egg, cow's milk, wheat, and soy. Histamine (1 mg/ml) was used as the positive and saline as the negative control. Atopy was defined as the presence of one or more positive skin prick tests with any allergen.

At 7 yrs of age, the pediatric allergist in each center, without knowledge of the subject's randomization or the results of the questionnaire or allergy skin tests nor participation in the care of the children or their families, examined the children using a structured questionnaire and made a clinical diagnosis of asthma, allergic rhinitis, and atopic dermatitis. The details of assessment had been described previously (7).

Ethics

Ethics Committees of the University of British Columbia and the University of Manitoba

approved the study. Parents signed informed consent and at year 7 children gave verbal consent.

Data analysis

Of the 380 children who returned for follow up, cord blood samples were available on 289 children; another five children with CB-IgE greater than 10 kU/l were excluded from the analysis because of possible contamination with maternal blood (3).

Analysis was carried out with cord blood IgE level dichotomized at the detection limit of 0.5 kU/l.

Bivariate relationships between CB-IgE level and the following familial and environmental factors were examined by chi-squared testing: maternal or paternal/sibling history of asthma, atopy in mother or father, gender, season of birth, birth order, race, maternal education, maternal age, exposure to parental smoking, and exposure to house dust mite allergen, cat and dog ownership before birth. Risk factors associated with high CB-IgE were determined using multiple logistic regression analysis with children's baseline characteristics and exposure to parental smoking, HDM level, dog, and cat ownership at year 1, and city and intervention allocation as covariates.

The following outcomes were assessed at 2 and 7 yrs by questionnaire: recurrent wheeze (defined as at least three episodes of wheeze in the past 12 months), food allergy (defined as a history of angioedema, urticaria, eczema, respiratory symptoms or vomiting or diarrhea within 4 h of ingestion of a recognized food allergen) and atopy. At age 7, pediatric allergist diagnoses of asthma, allergic rhinitis, and atopic dermatitis were also included as outcomes. To assess whether CB-IgE was an important determinant of these outcomes, multiple logistic regression analysis was performed using the various outcomes as the dependent variables adjusted for the above covariates.

Statistical analysis was carried out using STATA (STATA/SE 8.0, College Station, TX, USA) and SPSS/PC Version 15 (SPSS, Chicago, IL, USA).

Results

The number of families that dropped out was not significantly different between the two exposure groups, and children clinically assessed at 7 yrs of age were not different in baseline characteristics or exposures before birth compared with

those who did not return for follow up (data not shown).

CB-IgE was detectable (≥ 0.5 kU/l) in 55 (19.3%) of the 285 children. A significantly higher percentage of those with detectable CB-IgE had a maternal history of asthma, maternal atopy, and were born in the winter months compared with those with no detectable levels of IgE. (Table 1) After adjusting for the various characteristics using multiple logistic regression analysis, maternal atopy [adjusted OR 2.21 (1.01–4.84)] and birth in winter months [adjusted OR 4.07 (1.68–9.83)] remained significantly associated with high CB-IgE.

Table 1. Baseline characteristics of the birth cohort according to level of cord blood IgE

	<0.5 kU/l	≥ 0.5 kU/l	p-value
Race			
White	192 (83.5)	44 (80.0)	0.553
Non-white	38 (16.5)	11 (20.0)	
Sex			
Female	111 (48.3)	20 (36.4)	0.132
Male	119 (51.7)	35 (63.6)	
First born			
No	130 (56.5)	27 (49.1)	0.366
Yes	100 (43.5)	28 (50.9)	
History of asthma			
Father/sib	88 (38.3)	8 (14.5)	0.073
Mother	90 (39.1)	35 (63.6)	
Positive allergy skin test			
Father	144 (64.9)	34 (66.7)	0.871
Mother	147 (63.9)	44 (80.0)	0.025
Maternal education			
No secondary	48 (20.9)	17 (30.9)	0.151
Any secondary	182 (79.1)	38 (69.1)	
Maternal age			
Mean	32.1 $\pm$ 4.93	30.5 $\pm$ 6.0	0.084
City			
Vancouver	111 (48.3)	20 (36.4)	0.132
Winnipeg	119 (51.7)	35 (63.6)	
Season of birth			
Winter	51 (22.2)	22 (40.0)	0.036
Spring	79 (34.3)	11 (20.0)	
Summer	48 (20.9)	10 (18.2)	
Fall	52 (22.6)	12 (21.8)	
Exposure to smoking*			
Father/others	42 (18.3)	11 (20.0)	0.847
Mother	20 (8.7)	4 (7.3)	1.000
Before birth*			
HDM <2 μ g/g dust	160 (69.9)	34 (61.8)	0.249
≥ 2 μ g/g dust	69 (30.1)	21 (38.2)	
Before birth cat ownership			
No	176 (76.5)	44 (80.0)	0.721
Yes	54 (23.5)	11 (20.0)	
Before birth dog ownership			
No	195 (84.8)	44 (80.0)	0.415
Yes	35 (15.2)	11 (20.0)	

*Smoking data were available for 284 parents and HDM levels were measured in 284 homes of children who had cord blood IgE measurement.

Bold = significance with $p < 0.05$.

Table 2 shows the crude and adjusted odds ratios from multiple logistic regression analysis for the outcomes at year 2 and 7 according to whether or not CB-IgE levels were detected. After adjustment for baseline characteristics and other exposures, detectable levels of CB-IgE were associated at age 7 yrs with significantly increased risks for atopy [OR 2.22 (1.11, 4.41)], positive skin test reactions against any aeroallergen [OR 2.25 (1.13–4.47)], and recurrent wheeze [OR 2.51 (1.09, 5.76)].

Discussion

The most important finding in this study is the significant association of detectable CB-IgE with allergic sensitization to aeroallergens and recurrent wheeze at year 7. Our results are in accord with a number of studies (2, 3) but at variance with others (4, 5). The discrepancy in findings between studies could be related to several factors including the population studied, the variable limits of detectable CB-IgE, the duration of follow-up, environmental factors and the definition of asthma or other allergic diseases. Croner and colleagues (2) demonstrated that children with high CB-IgE had a fivefold risk for developing bronchial asthma in a follow-up study at 11 yrs of age. Our finding that detectable CB-IgE was not associated with an increased risk for recurrent wheeze at age 2 yrs but was associated with a significant increased risk at age 7, (though not a diagnosis of asthma) is consistent with that of Sadeghnejad (4) who reported detectable CB-IgE to be a risk factor for asthma at age 10 yrs, but not earlier.

This study also found that high CB-IgE level was associated with maternal allergen sensitization as in other studies (9, 10). Our finding that variation in cord blood IgE by season of birth with the peak in winter has also been reported (4), while another study showed a peak in late autumn (2). The relationship between the season of birth and cord blood IgE suggests possible exposure to inhalant allergens in-utero or shortly after birth. These findings suggest that the same familial and environmental exposures that lead to increased maternal sensitization also play a role in determining CB-IgE levels.

We did not measure IgA levels in the cord blood as a marker of maternal blood contamination, but used the approach of excluding samples with IgE higher than 10 kU/l, as suggested by other investigators (8). Although the sample size we used was relatively small compared with others, our study has the advantage of being of prospective design with well-characterized

Table 2. Cord blood IgE level by respiratory and allergic outcomes determined at years 2 and 7

Outcome	<0.5 kU/l n = 230	≥0.5 kU/l n = 55	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*	p-value	R ²
Year 2 outcome						
Recurrent wheeze	20 (8.8)	5 (9.3)	1.06 (0.38–2.95)	1.04 (0.32–3.32)	NS	0.138
Rhinitis	35 (15.4)	12 (22.2)	1.57 (0.75–3.27)	0.79 (0.30–2.08)	NS	0.329
Atopic dermatitis	25 (11.0)	6 (11.3)	1.03 (0.40–2.66)	1.38 (0.49–3.94)	NS	0.086
Food allergy						
Urticaria	32 (14.2)	12 (22.2)	1.73 (0.82–3.64)	2.15 (0.91–5.09)	NS	0.185
GI symptoms	26 (11.0)	10 (18.9)	1.88 (0.84–4.29)	2.21 (0.91–5.36)	NS	0.089
Atopy						
Any allergen	34 (15.1)	12 (22.2)	1.61 (0.77–3.35)	1.83 (0.81–4.11)	NS	0.072
Any food allergen	26 (11.6)	8 (14.8)	1.33 (0.57–3.12)	1.71 (0.65–4.49)	NS	0.109
Any aeroallergen	10 (4.4)	7 (13.0)	3.20 (1.16–8.84)	2.90 (0.94–8.95)	NS	0.133
Year 7 outcome						
Recurrent wheeze	24 (10.4)	14 (25.5)	2.93 (1.40–6.13)	2.51 (1.09–5.76)	0.029	0.136
Food allergy	13 (5.7)	4 (7.3)	1.31 (0.41–4.18)	1.54 (0.43–5.49)	NS	0.081
Asthma	36 (15.7)	14 (25.5)	1.84 (0.91–3.71)	1.54 (0.70–3.40)	NS	0.123
Allergic rhinitis	64 (27.8)	18 (32.7)	1.26 (0.67–2.74)	1.19 (0.59–2.40)	NS	0.138
Atopic dermatitis	30 (13.0)	9 (16.4)	1.30 (0.56–2.93)	1.08 (0.43–2.72)	NS	0.144
Atopy						
Any allergen	91 (41.2)	34 (64.2)	2.55 (1.37–4.76)	2.22 (1.11–4.41)	0.023	0.144
Any food allergen	24 (10.9)	11 (20.8)	2.14 (0.98–4.72)	2.36 (0.97–5.79)	NS	0.105
Any aeroallergen	90 (40.7)	34 (64.2)	2.60 (1.39–4.85)	2.25 (1.13–4.47)	0.021	0.149

Adjusted OR: baseline characteristics-race, sex, birth order, family history of asthma, medical education, city of residence, treatment allocation, season of birth were forced in while exposure variables: parental smoking, cat and dog ownership, HDM >= 2 µg dust were entered stepwise into the model.

Bold = significance with p < 0.05.

environmental exposures. Another limitation is that we did not use such corrections for testing multiple outcomes as Bonferroni's, but rather listed non-statistically significant associations as well.

In conclusion, our finding of association of high CB-IgE and sensitization to aeroallergens and recurrent wheezing illness in later childhood suggests that there may be a role for screening infants for CB-IgE. This may facilitate targeting early preventive measures for infants at higher risk for asthma based on family history.

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