

Parental history of atopic disease and concentration of cord blood IgE

C. C. JOHNSON, D. R. OWNBY* and E. L. PETERSON

Division of Biostatistics, Research Epidemiology and Medical Informatics and *The Allergy Research Laboratory, Department of Pediatrics, Henry Ford Health System, Detroit, USA

Summary

Background A family history of atopy, and cord blood immunoglobulin E concentration, have been shown to be predictors of atopic disease in children. Several studies have suggested that parental atopy may be related to newborn immunoglobulin E.

Objective The purpose of our analysis was to evaluate whether parental history of allergic disease was associated with cord blood immunoglobulin E concentration.

Methods The study subjects were from a defined population of 777 newborns delivered between 1987 and 1989. The mothers of these children completed a questionnaire during pregnancy concerning themselves and the child's father, including parental history of physician diagnosis of allergic diseases (allergies, hay fever and asthma). Total immunoglobulin E levels were quantitated in cord blood samples with an enzyme-linked immunoassay.

Results Median cord blood immunoglobulin E concentration was higher among infants whose mothers had a history of atopic disease, particularly for those with a history of asthma ($P < 0.022$) and allergen immunotherapy ($P < 0.016$) vs infants whose mothers had no history of any atopic disease. Comparing all babies with a maternal history of asthma, to babies where neither parent had a history of any atopic disease, the median cord blood immunoglobulin E was significantly higher (0.36 IU/mL vs 0.21 IU/mL; $P < 0.009$). This association was found only among female infants (0.49 IU/mL vs 0.20 IU/mL; $P < 0.001$).

Conclusion Maternal, but not paternal, history of atopic disease was associated with an elevated immunoglobulin E among newborns. For maternal asthma, this association was only evident in infant girls.

Keywords: cord blood IgE, family history, Carter effect, epidemiology

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Introduction

The familial nature of allergic disease is well known. Family history of atopic disease has been shown to be a relatively sensitive, but non-specific predictor of allergic diseases in children living in westernized countries [1–6]. Further, increasing serum concentration of IgE is generally associated with increasing risk of clinical allergic disease in children and adults [2,7–9] and some have reported that cord

IgE levels are related to the development of allergic disease and asthma in childhood [10–19]. Because of these associations it seems probable that parental history of allergic disease would be related to cord blood immunoglobulin E (IgE) concentration. Michel *et al.* [10] found that mothers, but not fathers, with a high serum IgE, had babies with higher cord IgE levels. Magnusson *et al.* reported data from a Belgian population of newborns showing that elevated cord blood IgE was associated with a maternal history of allergies [15]. One South African study has reported that a family history of atopy in first degree relatives of white newborn infants (mother, father or sibling) was statistically associated with elevated cord IgE [20]. We used data from a

Correspondence: Dr C. C. Johnson, Biostatistics, Research Epidemiology and Medical Informatics, One Ford Place, 3E Detroit, Michigan 48202, USA.

large, population-based, prospective study of children to evaluate whether reported parental history of atopic disease was associated with cord blood IgE concentration.

Materials and methods

The data used in this analysis were collected as part of an ongoing study evaluating environmental determinants of allergic diseases in a population of children followed from birth. Selection of the study cohort has been previously described in detail [21]. Briefly, all women 18 years and older, with a prenatal appointment at one of seven clinics serving the northern suburbs of Detroit Michigan, USA, were approached for study recruitment. To be eligible, a woman had to be a member of the Health Alliance Plan health maintenance organization and have an estimated date of confinement between 15 April 1987 and 31 August 1989, with delivery planned for one of the three hospitals serving the health maintenance organization patients. Additionally, women had to reside within an area surrounding the clinics as defined by contiguous postcodes.

Research nurses recruited women during midterm prenatal visits. At this time, the women completed a self-administered questionnaire concerning themselves and the babies' fathers. The following independent variables were collected in this manner: demographics, selected lifestyle characteristics including current smoking behaviours, and parental history of physician diagnosis of allergic diseases (allergies, hay fever and asthma), as well as bronchitis and emphysema. In addition, the mother was asked if she had ever been clinically evaluated by an allergist, had allergy skin tests, or allergic immunotherapy.

The *a priori* dependent variables for this analysis included the newborn's cord IgE level and gender. At delivery a cord blood sample was obtained. The serum was separated and stored at -20°C until assay. Total IgE levels were quantitated as previously described with an enzyme-linked immunoassay (ELISA) [21]. This assay is a biotin-avidin amplified ELISA. The antibody used in both the capture and detecting steps was affinity-purified anti-human IgE (Kirkegaard & Perry Laboratories, Gaithersburg, MD, USA). When the anti-IgE was used as the detecting antibody, it was biotin-labelled.

Standard curves were constructed from appropriate dilutions of a patient serum that had been standardized against the US reference standard. The average net optical density produced by unknown samples was converted to international units (IU) of IgE by calculation from the computer-fitted standard curve. Six internal standards were included with each assay run. The routine sensitivity of the assay was 0.02 IU/mL of IgE, and the average interassay coefficient of variation was 17.6%, an acceptable magnitude as we were measuring extremely low IgE levels.

Similarly, the concentration of IgA was measured by ELISA to evaluate possible contamination of the cord sera with maternal blood. Sera with IgA values of $>39\text{ }\mu\text{g/mL}$ were considered potentially contaminated with maternal blood and excluded from analyses [21].

Delivery data such as gender, as well as type of delivery, birth weight and length, and complications, were abstracted from the newborn's medical record. In the case of multiple pregnancies or births during the study period, only one child per family was eligible for study.

Statistical methods

Cord blood IgE concentrations were positively skewed, indicating non-normality. The IgE values were transformed via natural logarithm, yielding geometric means, but the data still exhibited non-normality. Therefore medians were compared, using the nonparametric Wilcoxon Rank Sum test. (The geometric means are also provided to allow comparison with other studies.) We analysed the cord IgE concentrations among newborns whose mothers or fathers reported a history of each atopic condition vs newborns with the specified parent having none of these conditions. Focussing on asthma, this analysis was repeated stratifying by parental smoking status. Differences in cord blood IgE among newborns for whom both parents had asthma, versus a single parent with asthma, were compared with newborns for whom neither parent had a history of asthma or any atopic disease. This analysis was repeated stratifying by infant gender.

Results

Of the 1194 pregnant women potentially eligible for inclusion in the study, 1090 (91%) were contacted; 953 (87%) agreed to participate. Cord blood was obtained and tested from 847 newborns (89%); others were not collected due to eventual miscarriage or stillbirth, complications at delivery, change of hospital for delivery, or inadvertent lack of specimen collection. Six of the bloods with high IgE concentrations were found to have high IgA levels; these specimens were considered to be contaminated with maternal blood and excluded. Ninety-two per cent ($n = 777$) of the remaining 841 mothers classified themselves as white; since there were insufficient numbers in the other ethnic groups, all analyses were restricted to whites. The mean maternal and paternal ages, with their standard deviations (SD), were 28.7 (SD 4.4) and 31.0 years (SD 5.5), respectively. Nearly all parents (96%) had a high school education, and over a third were college graduates. At the time of questionnaire administration, 82.0% of the mothers and 74.9% of the fathers were reported to be non-smokers.

Nearly a third of the mothers and a quarter of the fathers had a history of a physician diagnosis of allergies (Table 1). Less than 10% were documented to have a history of asthma. Fifteen per cent of the mothers had had an allergic disease diagnosed by an allergist, and 53% of these women gave a history of receiving allergen immunotherapy.

Cord blood IgE level was not related to educational status of parents, length of gestation, gender of baby, birth weight or length, or APGAR scores. Table 1 compares the median levels of cord blood IgE among newborns whose mothers or fathers had a positive history in each of the different categories of atopic disease to those newborns whose mothers and fathers, respectively, had a negative history of any atopic disease. For each maternal atopic disease-related category, the median cord IgE was higher for children whose mother had a positive response. This difference was statistically significant for a history of any allergy, asthma, or allergen immunotherapy. The cord blood IgE values were somewhat lower in babies whose fathers had a reported history of any allergies ($P < 0.081$) or hay fever ($P < 0.082$), and nearly identical for those babies with and without fathers with asthma.

Respiratory symptoms resulting from cigarette smoking may be misdiagnosed as allergic symptoms, or smoking may aggravate allergic symptoms and bring them to clinical attention. Smokers with chronic cough may also be misclassified as having asthma. Because of the possibility that smoking status may have influenced disease classification,

we examined the relationship between parental history of asthma and cord IgE by smoking status. Table 2 reveals that the positive association of maternal history of asthma with elevated cord IgE is evident only among babies of non-smoking mothers ($P < 0.006$); indeed compared with non-smokers, median IgE was lower among babies whose mothers or fathers had a history of asthma and were smokers. However, reclassifying those who smoke as negative for history of asthma, or excluding them from the analysis, did not noticeably alter the overall association between maternal asthma and higher cord blood IgE concentrations.

The median cord IgE was compared between those babies for whom both parents were positive for a history of asthma vs those babies for whom both parents had negative histories (Table 3). There was no difference, (0.19 IU/mL vs 0.21 IU/mL, respectively), although the number of children with two positive parents numbered only six. Similar analyses (both parents positive asthma history, maternal history only, and paternal history only, vs negative parental history) are presented for male and female infants separately. The association of a positive maternal history and higher cord IgE concentration was only apparent, and markedly so, among the female babies (0.49 IU/mL vs 0.20 IU/mL, $P < 0.001$).

Discussion

We expected to find that parental history of atopic disease

Table 1. Comparison of cord blood IgE levels among newborns, by maternal ($n = 777$) and paternal ($n = 772$) history of physician-diagnosed atopic diseases

	Positive history				No history of any atopic disease*				P-value
	n	Geometric mean cord blood IgE	Median cord blood IgE	Range**	n	Geometric mean cord blood IgE	Median cord blood IgE	Range**	
<i>Maternal</i>									
Physician diagnosis of any allergy	240	0.23	0.25	0.03–1.23	491	0.19	0.21	0.01–1.27	0.043
Physician diagnosis of hay fever	124	0.22	0.24	0.01–1.10	491	0.19	0.21	0.01–1.27	0.224
Physician diagnosis of asthma	56	0.26	0.33	0.05–1.25	491	0.19	0.21	0.01–1.27	0.022
Allergist confirmation of atopic disease	118	0.22	0.24	0.02–1.10	491	0.19	0.21	0.01–1.27	0.317
History of immunotherapy	63	0.28	0.31	0.06–1.10	491	0.19	0.21	0.01–1.27	0.016
<i>Paternal</i>									
Physician diagnosis of allergies	185	0.18	0.19	0.01–1.18	452	0.21	0.22	0.02–1.20	0.081
Physician diagnosis of hay fever	143	0.16	0.19	0.01–0.99	452	0.21	0.22	0.02–1.20	0.082
Physician diagnosis of asthma	49	0.22	0.23	0.04–1.35	452	0.21	0.22	0.02–1.20	0.645

* The comparison group is defined as children for whom the respective parent had a negative history of asthma or any allergy.

** Range runs from 5th to 95th percentile of data.

Table 2. Cord blood IgE levels among newborns, by parental history of asthma and current parental smoking behaviour*

	Positive history of asthma				No history of any atopic disease**				<i>P</i> -value
	<i>n</i>	Geometric mean cord blood IgE	Median cord blood IgE	Range****	<i>n</i>	Geometric mean cord blood IgE	Median cord blood IgE	Range****	
<i>Non-smokers</i>									
Maternal history of asthma	51	0.29	0.34	0.05–1.25	392	0.20	0.22	0.01–1.35	0.006
Paternal history of asthma	37	0.26	0.23	0.06–1.41	326	0.20	0.22	0.02–1.25	0.329
<i>Smokers~~</i>									
Maternal history of asthma	5	0.12	0.09	0.05–0.52	98	0.18	0.19	0.01–0.99	0.197
Paternal history of asthma	11	0.21	0.20	0.01–0.64	123	0.22	0.20	0.05–1.05	0.289

*Four newborns are excluded as one of their parents had an unknown smoking status (one father with a history of asthma and one mother and three fathers with negative histories of asthma or any atopic disease).

** The comparison group is defined as children for whom the respective parent had a negative history of asthma or any atopic disease.

*** Range runs from 5th to 95th percentile of data.

~~ Smokes one or more cigarettes a day at time of survey.

would be associated with an increased cord blood IgE concentration, suggesting an inherited tendency toward a higher basal serum IgE concentration. The significant association between positive maternal histories for atopic diseases and higher cord IgE concentrations supported this expectation. However, the inverse associations between

paternal history of any allergy or hay fever and the lack of an association with paternal history of asthma, which has been suggested in other studies [10,15], is intriguing.

Perhaps this apparent difference in the influence of maternal vs paternal allergic disease history is an example of the 'Carter effect', first described in childhood pyloric

Table 3. Cord blood IgE levels among newborns, by parental history of asthma and gender of baby*

	Positive history of asthma				No parental history of any atopic disease**				<i>P</i> -value
	<i>n</i>	Geometric mean cord blood IgE	Median cord blood IgE	Range""	<i>n</i>	Geometric mean cord blood IgE	Median cord blood IgE	Range""	
<i>All babies</i>									
Both parents with history	6	0.18	0.19	0.06–0.32	618	0.19	0.21	0.01–1.20	0.706
Maternal history only	48	0.28	0.36	0.05–1.25	618	0.19	0.21	0.01–1.20	0.009
Paternal history only	42	0.23	0.26	0.04–1.35	618	0.19	0.21	0.01–1.20	0.274
<i>Male infants (n = 344)</i>									
Both parents with history	5	0.18	0.18	0.06–0.32	297	0.22	0.23	0.02–1.40	0.543
Maternal history	21	0.18	0.25	0.01–0.47	297	0.22	0.23	0.02–1.40	0.976
Paternal history	22	0.25	0.29	0.04–1.35	297	0.22	0.23	0.02–1.40	0.282
<i>Female infants (n = 369)</i>									
Both parents with history	1	0.20	0.20	0.20–0.20	321	0.18	0.20	0.01–0.99	0.966
Maternal history	27	0.40	0.49	0.05–2.10	321	0.18	0.20	0.01–0.99	0.001
Parental history	20	0.21	0.22	0.05–1.81	321	0.18	0.20	0.01–0.99	0.638

* Two mothers with a positive asthma history had children with fathers with an unknown history of asthma; these couples' newborns were excluded.

** The comparison group is defined as children with both parents having a negative history of any atopic disease.

*** Range runs from 5th to 95th percentile of data.

stenosis [22]. The Carter effect is considered to be evidence in favour of a polygenic mode of inheritance, and is characterized by the finding that, in a condition in which the sex ratio differs from unity, the condition is found to be more common among the relatives of the less frequently affected sex. Carter proposed the scenario of polygenic inheritance in which the predisposing genes are distributed equally among males and females, but the number of genes required to produce manifestations of disease is higher in one sex. Thus, the condition would be less common in one sex, but affected individuals of that sex would have more predisposing genes, which they would have a higher probability of transmitting to their offspring. Happle and Schnyder demonstrated the Carter effect for asthma and atopic dermatitis [23]. In the case of allergic disease, affected women may have inherited more genes and thus be more likely than affected men to pass a sufficient number of genes to their children. If cord blood IgE level can be considered a marker for the later development of atopic disease, which is more common in boys, the Carter effect could explain the finding that mother's history of clinical disease, but not fathers, is associated with higher cord IgE. Another possibility is that atopic mothers may transplacentally pass cytokines, resulting in increased fetal IgE production.

Neither the Carter effect, nor transplacentally passed cytokines, explain the apparent restriction to female infants of the association between maternal asthma and higher cord blood IgE. We have not been able to hypothesize a biological mechanism that would explain this result except to suggest that sex hormones may play an influential role in the relationship between inherited characteristics and the prenatal production of serum IgE. A French study carried out in 1980 reported that progesterone therapy during pregnancy significantly increased mean IgE level in the cord blood of newborns [6].

We considered the possibility that a systematic misclassification bias may have been introduced if symptoms of smoking were erroneously identified as symptoms of allergic disease. When the comparison was restricted to non-smokers, the median cord IgE concentrations of infants born to mothers with a history of asthma compared with no maternal history of atopic disease remained significantly elevated. (Just the opposite was found among the small number of children whose mothers had asthma and smoked, suggesting that maternal smokers may have been misclassified as having asthma.) Similar analyses for fathers did not indicate a difference. We were unable to detect an association between parental smoking and cord IgE in this study population [21].

Another limitation of the study is that the information collected prior to delivery regarding the father's disease and smoking history was indirectly obtained through the mother. However, we have followed the majority of these children

over a 6 year period, and have usually had the opportunity to collect information from both parents. We have found the data regarding parental history of atopic disease and smoking behavior to be remarkably consistent.

The children in this cohort are being followed through their seventh birthday, at which time they are undergoing a clinical examination, pulmonary function testing, and skin tests. Future analyses will allow us to assess whether both parental history of atopic disease and cord IgE level are associated with the later development of asthma or other allergies in these children.

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