

Prematurity at birth reduces the long-term risk of atopy

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Background: Antigen exposure in early life has long-lasting effects on atopic sensitization. Thus the predisposition to atopy of children born preterm can be assumed to differ from that of children born at term.

Objective: The aim of this study was to evaluate the association between premature birth and atopy.

Methods: At an outpatient clinic, we examined 2 groups of 10-year-old children, 72 who were born preterm (birth weight < 1500 g) and 65 who were born at term (birth weight > 2500 g). The atopy data were collected with a questionnaire, by performing skin prick testing, and by measuring the serum total IgE level, 3 allergen-specific IgE levels, the eosinophil cationic protein level, and the blood eosinophil level. The data on perinatal and neonatal events affecting the preterm children were collected from the hospital records.

Results: By the age of 10 years, the children born preterm had significantly less atopy than the children born at term: 15% versus 31% of children in the 2 groups were defined as having had obvious atopy ($P = .03$, odds ratio 0.41, 95% CI 0.18-0.93). The mean value of total IgE level was significantly higher in the term group, 74 kU/L versus 41 kU/L ($P = .02$). By skin prick testing, the children born at term had positive reactions 2 to 3 times more often; 37% versus 17% of children in the groups had at least 1 positive reaction ($P = .007$).

Conclusion: Our data show that prematurity at birth is linked with a decreased long-term risk of atopic sensitization. (*J Allergy Clin Immunol* 2001;107:229-34.)

Key words: Atopy, allergy, gestational age, prematurity, infant, newborn, school-aged, long-term

In atopic diseases the priming of the immune system is shown to be based markedly on antigen exposure in early life, or even during gestation.¹⁻⁵ Preterm infants encounter the environment during their first weeks in a different immunologic stage than term infants do: their immune system is less mature,⁶ and the gut more permeable to macromolecules.⁷⁻¹⁰ Because of the immaturity and mechanical treatments, preterm infants are more susceptible to early infections. They are also given earlier supplementary feeding and are exposed at the hospital to different environmental antigens (microbial milieu, tobacco

Abbreviations used

ECP: Eosinophil cationic protein

OR: Odds ratio

SPT: Skin prick test

smoke, animal dander) than in a normal home environment. Consequently, the atopic predisposition of children born preterm can be assumed to differ from that of children born at term, but knowledge about this aspect is scanty. Only a few studies have been made, and the results have not resulted in any uniform conclusion.¹¹⁻¹⁸ Exposure of an immature immune system to environmental antigens has previously been commonly considered to lead to more frequent sensitization rates,¹⁹ but in recent epidemiologic studies^{15,16} low gestational age has been found to relate to a decreased risk of atopic disorders.

Apart from atopy, the long-term pulmonary outcome of children born preterm has been studied widely, and preterm infants have been found to have an increased risk for bronchial obstruction and hyperreactivity.²⁰⁻²³ The pathogenesis of these long-term pulmonary sequelae is not precisely known but is obviously multifactorial^{20,24,25} and different from the pathogenesis of asthma. Thus analysis of the obstructive pulmonary findings is restricted in this article.

The aim of this study was to evaluate the possible long-term effects of prematurity on atopic predisposition.

METHODS

Study groups

We collected data from the hospital records of 100 consecutive prematurely born children (58 boys, 42 girls) with birth weights less than 1500 g. The children were born in 1987 to 1988 and were treated in the neonatal intensive care unit at the Hospital for Children and Adolescents, University of Helsinki. The control group consisted of 96 unselected 10-year-old children (55 boys, 41 girls) from 2 schools in the Helsinki region (3 classes from an urban and 1 from a rural school). All of the children from the classes whose birth weight was more than 2500 g were invited. Birth weights of all children born in Finland are available at schools and are transferred from child health clinics. The age and sex distributions of the groups invited were equivalent.

Seventy-two percent of the preterm group (46 boys, 26 girls) and 68% of the term group (34 boys, 31 girls) participated. The mean gestational age ($\pm$ SD) of the children born preterm was 28.5 ± 2.4 weeks (range 23.4-33.7 weeks). In the term group, gestational ages could not be recorded. The mean birth weight ($\pm$ SD) of the children born preterm was 1075 ± 271 g (range 550-1500 g) and of the children born at term was 3593 ± 470 g (range 2540-5200 g; only 2 children weighed < 2900 g). Among the children born preterm the

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TABLE I. Environmental factors in the 2 groups of patients at birth and at 10 years of age and the differences between the groups

Environmental factor	Preterm group (n = 72)		Term group (n = 65)		P value	
	At birth	At 10 y	At birth	At 10 y	At birth	At 10 y
Mean No. of children in family	2.0	2.3	1.7	2.6	.151*	.185*
Furred pets at home	17%	44%	26%	45%	.175†	.984†
Smoking of parents	26%	26%	34%	29%	.341†	.711†
Home locality					.920†	.584†
Rural nonfarm	21%	24%	22%	28%		
Urban	79%	76%	78%	72%		

*Mann-Whitney test.

† χ^2 test.

mean length of hospital stay in the neonatal period was 3.0 ± 2.5 months (range 1.0-14.2 months). The mean age at the time of the examination was 10.1 years in both groups (in the preterm group, $SD \pm 0.3$ and range 9.6-10.8 years; in the term group, $SD \pm 0.4$ and range 9.4-10.9 years). There were no significant differences between the groups in sex distribution, month of birth, month of examination, parental educational level (data not shown), or environmental background factors (Table I).

Data collection and definitions of atopy

Exact data of pregnancy and delivery and of early medical problems, treatments, and nutrition were collected from the case records of the children born preterm. Both groups of children were invited to 1 visit at the outpatient clinic of the Hospital for Children and Adolescents, University of Helsinki. Parents were asked to fill out a questionnaire on possible risk factors for atopy. The questionnaire was checked at the outpatient clinic by having parents discuss the questions in detail with one of the authors. The physical examination of the children was carried out by the same author (M.S.).

Atopic eczema was diagnosed if the child had a history of chronic or chronically relapsing itching dermatitis with typical morphology and distribution.²⁶

Diagnosis of allergic rhinoconjunctivitis was based on a history of runny and/or blocked nose and/or itchy, watery eyes with seasonal variation or with animal contacts and apart from infection episodes.

Diagnosis of asthma was confirmed when bronchial obstruction reversed by a bronchodilator had been recorded at least 3 times and recorded at least once by a physician. To determine the respiratory symptoms of an atopic nature from all of the long-term respiratory sequelae, we considered the child as having had atopic asthma if she or he had, in addition to the asthma diagnosis, at least 1 objective finding of an atopic reaction measured in the study: serum total IgE level more than 320 kU/L, at least 1 allergen-specific IgE level greater than 0.8 kU/L, or at least 1 positive reaction to the skin prick test (SPT).

The child was considered to be atopic if she or he had had at least 1 of the above-mentioned symptoms (symptoms in at least 1 organ). When the history of atopic symptoms was validated with at least 1 objective finding of an atopic reaction (as in the definition of atopic asthma), the child was classified as having obvious atopy.

A family history of atopy was defined as asthma, allergic rhinoconjunctivitis, and/or atopic eczema in 1 or both parents (symptoms in at least 1 organ). A family history of definitive atopy was recorded if 1 or both parents had had asthma or symptoms in more than 1 organ.

Laboratory methods

SPTs were performed by 2 experienced nurses at the hospital. The test consisted of a panel of 8 standard Soluprick solutions from Allergologiska Laboratorium (Copenhagen, Denmark): extracts of birch, timothy, meadow fescue, and mugwort pollen; cat and dog dander; house dust mite *Dermatophagoides pteronyssinus*; hen's

egg; and latex prick test standard solution from Stallergenes SA (Antony Cedex, France). Histamine hydrochloride (10 mg/mL) served as a positive control and 50% glycerol solution as a negative control in testing. The reaction was regarded as positive when the wheal diameter was 3 mm or more and the negative control solution caused no reaction.

The serum total IgE concentration and the allergen-specific IgE antibodies to hen's egg, cat, and birch were measured by enzymatic UniCAP fluoroimmunoassay, and serum eosinophil cationic protein (ECP) level was measured by UniCAP fluoroimmunoassay (Pharmacia-Upjohn, Uppsala, Sweden). Blood eosinophils were also counted. A serum total IgE level greater than 320 kU/L, an allergen-specific IgE antibody level greater than 0.8 kU/L, an ECP concentration greater than 18 μ g/L, and a blood eosinophil count of greater than $0.40 \times 10^9/L$ were considered to indicate atopic sensitization.

Statistical methods

Statistical analyses were done with SPSS release 8.0 for Windows, standard version. Categorical variables were analyzed by the Pearson χ^2 test, and continuous data were analyzed by the Mann-Whitney test or the Student *t* test after log transformation. Odds ratios (ORs) with 95% CIs were calculated by logistic regression. The multiple logistic regression method with a forward stepwise model was used to analyze potential independent associations of several risk factors of atopy and to test the effects of potential confounding factors. The possible associations of background factors with atopy were analyzed separately in the groups. The series was unpaired, and the significance of the test results was interpreted as 2 sided. *P* values of .05 or less were considered statistically significant.

Ethics

The study was approved by the Ethics Committee of the Hospital for Children and Adolescents, University of Helsinki.

RESULTS

Atopic findings in the groups

The frequency of atopy was significantly lower in the preterm than in the term group: 31% versus 49%, respectively, of children were found to be atopic. The same significant difference was found when the stricter criteria of obvious atopy were used: 15% of preterm and 31% of term children had obvious atopy. Also, the incidences of the separate atopic symptoms, atopic eczema and allergic rhinoconjunctivitis, were lower in the preterm than in the term group, but the differences did not reach statistical significance (Table II). Atopic asthma was equally common in both groups, whereas asthma without emphasis on atopy was more common in the preterm group (17% vs 8%, *P* = .11).

TABLE II. Cumulative incidences of atopic symptoms in percentages in the 2 groups, as well as the differences between the groups

Symptom	Preterm group (n = 72)	Term group (n = 65)	P value*	OR†	95% CI
Atopic eczema	22.2	35.4	.088	0.52	0.25-1.11
Allergic rhinoconjunctivitis	19.4	33.8	.056	0.47	0.22-1.03
Atopic asthma‡	5.6	6.2	1.0	0.89	0.21-3.74
Atopy§	30.6	49.2	.026	0.45	0.23-0.91
Obvious atopy	15.3	30.8	.030	0.41	0.18-0.93

Boldface indicates significant difference between the groups.

* χ^2 test.

†Logistic regression method.

‡Asthma with serum total IgE level > 320 kU/L, at least 1 allergen-specific IgE level > 0.8 kU/L, or at least 1 positive SPT reaction.

§Atopic eczema, allergic rhinoconjunctivitis, and/or atopic asthma (atopic symptoms in at least 1 organ).

||Atopic symptoms in at least 1 organ and serum total IgE level > 320 kU/L, at least 1 allergen-specific IgE level > 0.8 kU/L, or at least 1 positive SPT reaction.

The mean level of serum total IgE was significantly higher in the term group (Table III), and with SPTs the children born at term were 2 or even 3 times more likely to have positive reactions to the tested allergens (Table IV). With comparison of the frequencies of 1, 2, and 3 positive SPT reactions among the 9 in the panel, significant differences in all categories were again clearly seen between the groups. The same trend was observed when positivity for serum allergen-specific IgE antibodies was analyzed (Table IV).

Background factors associated with atopy in the groups

In univariate logistic regression analysis, we assessed the possible associations between atopy and the following background factors in the groups: sex, morbidity due to frequent respiratory infections during first 2 years (>6 episodes of infections in 6 months), parental atopy and educational level, number of children in the family, presence of furred pets at home, parental smoking, and type of home locality during the first and the current year. The only factor significantly associated with atopy in both groups was parental atopy (preterm group: $P = .020$, OR 3.68, 95% CI 1.23-10.99; term group: $P = .0002$, OR 13.11, 95% CI 3.32-51.81).

Apart from this, we observed a difference in parental atopy between the groups: allergic rhinoconjunctivitis was significantly more common in the parents of the children born at term. Asthma and atopic eczema, however, were equally common, and when the atopic symptoms were analyzed together, no significant difference was found in family history of atopy between the groups (Table V).

The proportion of children who had had frequent respiratory infections during the first 2 years was significantly higher in the preterm than in the term group: 42% versus 15% ($P = .001$). The same difference was observed in the frequencies of adenotomy and tympanotomy: 58% of the preterm group and 31% of the term group had had these operations ($P = .001$). Respiratory infection morbidity, however, was not found to be independently associated with atopy in the groups (data not shown).

TABLE III. Geometric means and 95% CIs of values of blood eosinophil count (EOS), serum total IgE level, and serum ECP level in the 2 groups, as well as the differences between the groups

	Preterm group (n = 72)	Term group (n = 64)	P value*
Blood EOS (10 ⁹ /L)	0.16 (0.12-0.20)	0.17 (0.13-0.22)	.733
Total IgE (kU/L)	40.7 (28.9-57.4)	74.3 (51.5-107.2)	.020
Serum ECP (μg/L)	6.8 (5.7-8.1)	8.9 (7.1-11.0)	.065

Boldface indicates significant difference between the groups.

*Student t test.

TABLE IV. Percentages of children in the 2 groups with positive SPT reactions to 9 standard test solutions and children with high serum allergen-specific IgE levels (>0.8 kU/L), as well as the differences between the groups as analyzed by the χ^2 test

	Preterm group	Term group	P value
SPT	n = 72	n = 65	
Birch	9.7	23.1	.034
Timothy	8.3	20.3	.069
Meadow fescue	11.1	26.2	.023
Mugwort	2.8	9.2	.108
Cat	5.6	16.9	.033
Dog	2.8	10.8	.059
<i>D pteronyssinus</i>	1.4	3.1	.452
Latex	1.4	0	
Egg	0	0	
≥1 positive reaction	16.7	36.9	.007
≥2 positive reactions	13.9	27.7	.045
≥3 positive reactions	5.6	20.0	.010
Serum specific IgE measurement	n = 72	n = 64	
Birch	11.1	20.3	.138
Cat	4.2	10.9	.190
Egg	0	3.1	.220
≥1 of the above 3 >0.8 kU/L	12.5	23.4	.095

Boldface indicates significant difference between the groups.

TABLE V. Percentages of parental atopic symptoms in the 2 groups and the differences between the groups

Symptoms in 1 or both parents	Preterm group (n = 72)	Term group (n = 65)	P value*	OR†	95% CI
Asthma	6.9	3.1	.445	2.35	0.44-12.55
Atopic eczema	29.2	30.8	.838	0.93	0.45-1.93
Allergic rhinoconjunctivitis	34.7	61.5	.002	0.33	0.17-0.67
Family history of atopy	51.4	66.2	.08	0.54	0.27-1.08
Family history of definitive atopy‡	15.3	21.5	.343	0.66	0.27-1.57

Boldface indicates significant difference between the groups.

* χ^2 test.

†Logistic regression method.

‡Asthma, allergic rhinoconjunctivitis, and/or atopic eczema in 1 or both parents.

§Asthma or symptoms of more than 1 organ in 1 or both parents.

Parental smoking during the first year of the child's life was found to be related to an increased risk of atopy but only in the term group ($P = .032$, OR 3.28, 95% CI 1.11-9.70). The effect of the type of home locality during the first year was also seen only in the term group: children living in an urban area had less obvious atopy than children living in a rural area, 24% versus 57% ($P = .020$, OR 0.23, 95% CI 0.07-0.80). In analysis of background factors between the 2 different home localities, no significant differences were found in parental atopy or smoking habits or in sibship size, but the number of families with furred pets and the level of paternal education differed significantly: furred pets were more common in the families living in rural areas, and fathers in urban areas were more highly educated (data not shown). Rural living in this study consisted of only nonfarm environments; no children in either group were living on a farm.

In the multivariate logistic regression analyses, however, the effect of the home locality in the term group became nonsignificant ($P = .15$), whereas the association between parental smoking and atopy remained in the model ($P = .02$, adjusted OR 14.1, 95% CI 1.49-131.9). Also, the significance of parental atopy as a risk factor remained expectedly in the multivariate analysis of both groups. The multivariate analyses were adjusted for all the background variables that were also analyzed separately by univariate methods.

Perinatal and neonatal treatments and events during the intensive care period were widely analyzed in the preterm group, but in the univariate analyses no single factor was found to be significantly associated with obvious atopy (data not shown). In the multivariate analyses, however, early feeding (before 2 weeks of age) with cow's milk-based formula or protein fortifier was found to relate weakly to an increased risk of obvious atopy, with a wide CI ($P = .045$, OR 18.9, 95% CI 1.07-335.7), and morbidity from respiratory distress syndrome was found to relate to a reduced risk of obvious atopy ($P = .035$, OR 0.05, 95% CI 0.003-0.81). The analyses were adjusted for family history of definitive atopy; gestational age; cause of preterm delivery; mode of delivery; durations of mechanical ventilation and oxygen therapy; morbidity due to respiratory distress syndrome, bronchopulmonary dysplasia, and blood culture-verified sepsis; feeding with cow's milk-based formula or protein fortifier before or after 2 weeks of age; and length of hospital stay ($n = 51$ after adjustment).

DISCUSSION

In our study prematurity was found to reduce the risk of the appearance of atopic symptoms and of development of IgE-mediated responses during the first 10 years of life. The cumulative incidences of atopy found in our study correlate well with the results of the recent epidemiologic studies, in which the lifetime prevalence of allergic disorders and their regional differences in Finnish children were evaluated.^{27,28} According to these studies 44% of 11,607 13- to 14-year-old children had had at least 1 atopic disorder, and in the Helsinki area the corresponding figure was 48%. The life-time prevalence of self-reported asthma was 4% to 8%, of allergic rhinitis 44% to 55%, and of itching dermatitis 24% to 28%. In our study in the term group, the corresponding figures were 49%, 8%, 34%, and 35%.

A few earlier studies concerning atopy among prematurely born children gave conflicting results: prematurity was related to either an increased¹¹⁻¹³ or a decreased risk of atopy,¹⁴⁻¹⁶ and in some studies no association has been found between gestational age and atopy.^{17,18} Von Mutius et al²⁹ found a difference in atopic predisposition only between girls who were born preterm and girls who were born at term: preterm girls who had been mechanically ventilated had less atopy than term girls. Direct comparisons between the studies are, however, hampered by differences in study designs, diagnostic definitions, and study populations. In several studies the mean birth weight and gestational age of the preterm children were higher than in our study.^{12,13,17,18}

Fetal immune responses to specific antigens increase with gestational age, which is documented in increasing levels of specific IgEs in cord blood and in increasing proliferative responses of cord blood mononuclear cells.⁶ Moreover, the defense factors of the intestine, both non-specific and immunologic, are less developed in preterm than in term infants.⁷⁻¹⁰ Immature immune and gastrointestinal systems have formerly been estimated to be more susceptible to atopic sensitization.¹⁹ Our present results, in contrast, show significantly lower atopic sensitization rates among children born very preterm. Differences in IgE-mediated reactions, measured by several indicators, including atopic symptoms, SPT reactions, serum total IgE levels, ECP levels, and allergen-specific IgE levels, provide strong evidence for our result. Which factors of

prematurity were responsible for the trend could not, however, be delineated in our study, but explanations can be sought from background factors that differ between the groups. The evaluation of background factors as possible risk factors for atopy in the groups was, however, hampered by the small sample size.

Factors relating to prematurity (pre-eclampsia, maternal glucocorticoid treatment, mode of delivery, neonatal infection) have been shown to modify the developing immune system.³⁰⁻³² In our study, only an early feeding pattern and respiratory distress syndrome were weakly associated with atopy. Early feeding with cow's milk-based formula or protein fortifier was found to increase the risk of atopy. Lucas et al³³ found a similar association but only in preterm neonates genetically at high risk. In an earlier study from our clinic, in contrast, feeding exclusively with breast milk was shown to increase the risk of atopy in preterm infants.¹⁸ Our current finding is consistent with the results of several studies in children born at term, which showed an increased risk of atopy related to early feeding with cow's milk.³⁴⁻³⁷ This result of an association between feeding and atopy cannot, however, be used in comparison of the 2 groups because the data from the term group are missing.

The intestinal colonization of preterm neonates is modified by the special hospital microbial flora and by different early feeding patterns, which have been shown to affect the intestinal bacterial flora.³⁸ Neonate immune systems are primed obviously also more often by severe neonatal infections. (In our series, 15% of the preterm children had had blood culture-verified sepsis during the intensive care period.) Considering the previous data showing that microbial agents have an important effect on atopic sensitization and induction of tolerance,^{39,40} the special neonatal microbial exposure of preterm infants can be assumed to have a partial role in inducing the postnatal maturation of their T_H cell system more toward the T_H1 cell line.

The results concerning the role of passive exposure to smoke and the type of home locality on atopic sensitization were interesting. Associations between these factors and atopy were seen only in the term group. Exposure to tobacco smoke was related to an increased risk of atopy, as also shown in many other studies,⁴¹ and urban living was related to a decreased risk of atopy, but only in the univariate analyses. In a recent epidemiologic Finnish study, a similar trend was reported in asthma prevalence between urban and rural nonfarm environments, whereas concurrently a childhood farm environment was found to independently reduce the risk of asthma and allergic rhinoconjunctivitis.⁴² One possible explanation for the lower sensitization rates of children born preterm to the above-mentioned factors is their avoidance of exposure in early life: preterm neonates are less exposed to passive smoke and obviously also to many other common inhaled allergens during their long neonatal hospital stay.

The trend for a slightly higher incidence of parental atopy in the term group emerged as a side observation in our study. Von Mutius et al²⁹ have reported a parallel

finding of difference in parental atopy between preterm and term boys. Our finding raises the question of a possible association between preterm delivery and parental atopy, especially when we consider the dominance of T_H2 cells during pregnancy, which is estimated to be essential for the successful outcome of pregnancy.⁴³ There is also some preliminary evidence that atopic mothers may create a more T_H2-oriented environment than nonatopic mothers.⁴⁴ The results of our study correspond well with this finding.

In conclusion, we found that prematurity at birth reduces the long-term risk of atopic sensitization. Further research is needed to define the factors and immunologic mechanisms behind the trend.

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