

Neonatal birch-pollen contact and subsequent allergy to birch pollen

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Summary

It is shown by regression analysis that the risk of immediate hypersensitivity to birch pollen, as measured by a skin test, is positively correlated with the quantity of birch male flowers and the number of non-rainy days in the first birch flowering season (May) met in infancy. The risk is also dependent on the month of birth, with maximal risk associated with birth in February–April. The results suggest that early pollen contacts, particularly during the first 6 months of life, increase the risk of pollen allergy for a period of 20 years. We estimate that elimination of early birch pollen contacts could have reduced the prevalence of immediate hypersensitivity to birch by 28% in our age group 0–19 years.

Introduction

It has been shown that the risk of developing pollen allergy (Björkstén & Suoniemi, 1976; Pearson, Freed & Taylor, 1977) and mite allergy (Morrison Smith & Springett, 1979) is dependent on the month of birth. This is probably due to a sensitive period early in life during which an environmental factor (or factors) and seasonal variation in this factor influence the development of subsequent allergy. In this study we have tried to investigate whether neonatal allergen contact could be such a factor.

We have looked for the effects of early exposure to pollen by examining the risk of immediate hypersensitivity to birch pollen as a function of both the month of birth and the intensity of the first pollen season. We chose the birch tree (*Betula* spp.), since flowering data were available, and the birch is a common tree in Southern Finland. Here, the birch pollen causes symptoms with a high prevalence approaching that of grass-pollen allergy (Haahtela, 1979).

Patients and methods

We examined retrospectively the records of patients aged 0–29 years, who had visited our hospital between January 1970 and May 1977. We found 2171 patients with a positive intradermal skin test to birch and alder (*Alnus* spp.), and these patients were included in the study. The age distribution is given in Table 1. Birch and alder-pollen

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Table 1. Number of patients by age and month of birth, and deviation of the month-of-birth distributions from those in corresponding reference groups

Month of birth	Age (years)				
	0-9	10-14	15-19	20-29	0-29
January	80	52	34	27	193
February	74	65	38	38	215
March	106	52	49	46	253
April	99	66	33	32	230
May	62	53	41	40	196
June	59	40	29	32	160
July	53	35	18	41	147
August	46	35	21	36	138
September	45	44	27	34	150
October	64	55	24	29	172
November	57	37	25	28	147
December	47	53	32	38	170
All months	792	587	371	421	2171
<i>P</i> *	< 10 ⁻⁵	0.005	0.026	0.686	< 10 ⁻⁵

* The month-of-birth distribution in patient and corresponding reference groups were compared using the χ^2 -test. The significance of differences is indicated by *P* values.

allergens are known to cross-react, and the sensitivities usually occur together (Belin, 1972). Both trees belong to the *Betulaceae* family. Discarding those who reacted to only one species is assumed to have eliminated for the most part weakly or falsely positive patients. We considered as negative any doubtful skin tests, e.g. those with a weal diameter less than half of that given by a 0.1 ml of 100 mg/l histamine dihydrochloride solution, or those marked with one plus.

Most of our patients come from the Uusimaa district around Helsinki. As a reference group we used all those born in Uusimaa in the same years as the patient (sub)-group under examination. The maximal reference group numbered 444 270 persons. The data were from the Central Statistical Office of Finland. The month-of-birth distribution in those born in Uusimaa was found to be nearly identical with that in the total population of Finland, which we have described previously (Björkstén & Suoniemi, 1976).

The (relative) risk R_j of developing immediate hypersensitivity to birch pollen in those born in period *j* was estimated using the equation

$$R_j = \frac{n_j/n}{N_j/N} \quad (1)$$

where n_j is the number of patients born in period *j*, *n* is the total number of patients, and N_j and *N* are the corresponding numbers in the reference group. By this definition, the risk in the total patient group (*n*) is 1.

The curve showing logarithms of relative risks (log *R*) in 1642 patients born in

12-month periods (1 July to 30 June) preceding and including each pollen season in 1955–1970 has a trend which causes a maximum to occur in the mid-sixties (Fig. 1). Logarithms were used, because the following multiplicative model was assumed to describe the sources of variation in risk:

$$R = T \times I \times E \quad (2)$$

In the equation T is a trend, I is yearly variation, and E is a residual component. In this study the trend is not of interest, but a confounding factor, which must be allowed for.

The least squares method was used to estimate the model

$$\log R = a_0 + a_1t + a_2t^2 + a_3t^3 + a_4t^4 + b_1M + b_2N \quad (3)$$

where the quartic in time (t) describes the trend component (Fig. 1). The birch male-flower quantities (M) and the number of non-rainy days (N) in May, the flowering season, were used to explain yearly variation.

Flower data were from two sample plots of *Betula pubescens* (in Tuusula and Vantaa) and two plots of *Betula verrucosa* (in Helsinki and Tuusula), all in Uusimaa. In each plot male flowers falling down from the trees after flowering were collected in one to ten funnels, and the dry weight for each plot and season was measured (Koski & Tallqvist, 1978). To make data from different plots comparable we transformed the dry-weight values to a zero-to-one scale with one denoting the male flower quantity for the plot in question in the top flowering year (1964).

The number of non-rainy days (precipitation < 0.1 mm) in May was obtained from the records of six weather stations in Uusimaa (Helsinki-Kaisaniemi, Helsinki-Malmi, Pohja, Tuusula, Vantaa and Vihti) (Finnish Meteorological Institute, 1955–1970). Averages for the plots (Fig. 3B) and the stations (Fig. 3C) were used for the model (eqn 3).

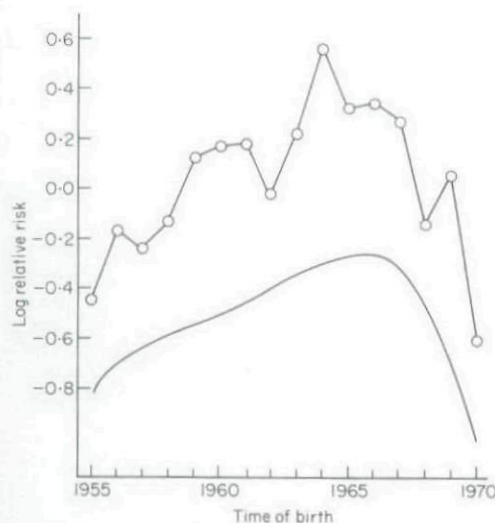


Fig. 1. Logarithm of the relative risk of immediate hypersensitivity to birch pollen as a function of the time of birth. The upper curve shows the risk ($\log R$) in patients born in 12-month periods (1 July–30 June) preceding and including each pollen season. The lower curve shows the trend ($q(t)$) as defined in the text.

Results

In children and teenagers the risk of developing immediate hypersensitivity to birch pollen, as measured by a skin test, was found to be dependent on the month of birth (Fig. 2). In the age group 0–19 years, the risk in those born at the most favourable time in July–August is 56% of the risk in those born in February–April, the period associated with maximal risk. Risk *vs* month-of-birth curves are rather similar for the age groups 0–9, 10–14, and 15–19, but in the age group 20–29 the month of birth no longer appears to affect the risk (Fig. 2 and Table 1). No sex difference could be found.

There is a trend in the risk *vs* time-of-birth curve, and this trend is due to the fact that mainly children and teenagers have been skin tested (Fig. 1). The yearly variation in risk—after removal of the trend component—is depicted by the curves in Fig. 3A. These may be compared with curves for birch male flower quantity (Fig. 3B) and for the number of non-rainy days (Fig. 3C) in the corresponding pollen season (May).

With the least-squares method we obtained the regression equation

$$\log R = q(t) + 0.417 M + 0.733 N \quad (4)$$

where R is the relative risk of birch-pollen hypersensitivity, $q(t)$ is a quartic in time describing the trend component, M is the male flower quantity, and N is the proportion of non-rainy days in May (number of non-rainy days/31). The regression coefficients of both M and N are significantly different from zero ($P=0.002$ and 0.004 , respectively, using one-sided t -tests). Good correlation is also apparent from Fig. 3A, where actual values for $\log R - q(t)$ and corresponding values estimated from variables M and N with eqn (4) are shown.

Closely similar results were obtained when quarterly instead of yearly risk data

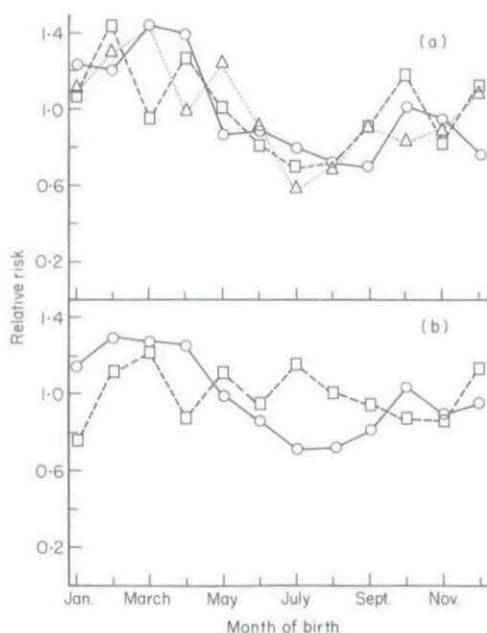


Fig. 2. Relative risk of immediate hypersensitivity to birch pollen as a function of the month of birth in various age groups. (A) $\circ$, 0–9 years; $\square$, 10–14 years; Δ , 15–19 years. (B) $\circ$, 0–19 years; $\square$, 20–29 years.

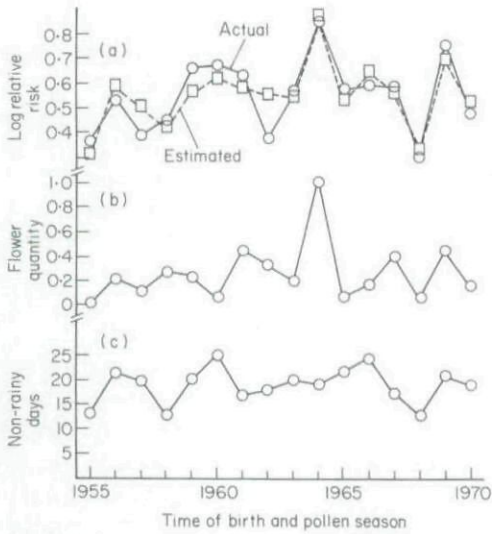


Fig. 3. Trend-adjusted logarithm of the relative risk ($\log R - q(t)$) as a function of the time of birth, and environmental variables in the corresponding years. (A) $\circ$, $\log R - q(t)$ values in patients born in 12-month periods (1 July–30 June) preceding and including each pollen season; $\square$, corresponding values estimated from flowering and rain level data with eqn (4). (B) Birch male-flower quantity. (C) Number of non-rainy days in May.

were first used in a trend-elimination procedure, and data were then fitted to the regression equation

$$\log R' = c_0 + c_1 M + c_2 N \quad (5)$$

where $\log R'$ is the trend-adjusted yearly mean of the logarithmic relative risk.

Discussion

The results (Table 1 and Fig. 2) and two previous reports (Björkstén & Suoniemi, 1976; Pearson, Freed & Taylor, 1977) indicate that the risk of developing pollen allergy is dependent on the month of birth. In this study we have also examined the dependence of the risk of immediate hypersensitivity to birch pollen, as measured by a skin test, on the intensity of the first pollen season met after birth. Unfortunately, regular pollen counts were not initiated in Finland until 1975, and our patients were born before this time. We have had to assume that the air-borne pollen quantity is dependent on the quantity of birch male flowers and the raininess during the flowering season in May; these variables have been recorded. Rain is known to remove effectively particulate matter from the air (Gregory, 1961).

Regression analysis shows that the risk of birch-pollen hypersensitivity has a positive correlation with the flower quantity and the number of non-rainy days in May in the first flowering season encountered (eqn 4 and Fig. 3). This observation and the month-of-birth effect provide, in our opinion, good statistical evidence in favour of neonatal pollen contact as a causal factor in subsequent birch-pollen allergy. It should be added that there must also be other factors.

If the proposed causal relationship is accepted, it can be concluded from Fig. 2 that babies aged 3 months or under are most susceptible to pollen contacts and that

susceptibility is substantially reduced by 6 months of age. It can also be estimated that if our entire population aged 0–19 had been born in July–August, *i.e.* if early birch pollen contacts had been greatly reduced, then the prevalence of positive skin tests could have been cut by 28%. Beyond 20 years, the month-of-birth effect is not regularly found (Table 1) (Björkstén & Suoniemi, 1976).

In a previous study we reported also that animal epithelium allergy was dependent on the month of birth (Björkstén & Suoniemi, 1976). Subsequently we have found that this observation cannot be regularly made, and conclude that the relation between epithelium allergy and month of birth is not yet established.

One possible objection is that allergy to birch has in this study been measured by skin tests alone. In the preceding study, however, we observed the month-of-birth effect in patients undergoing pollen hyposensitization and judged allergic to pollens by several criteria. Another objection is that we have not taken into account the effects of early alder-pollen contacts, though birch and alder allergens cross-react (Belin, 1972). In the period 1976–1978 cumulative pollen counts in Turku, Southern Finland, were 30 700/m³ for birch and only 2800/m³ for alder (Finnish Aerobiology Group, 1976–1978). In Uusimaa the birch covers approximately 13% and the alder 3% of forest land (Kuusela, 1967). Based on this and clinical experience, we feel that alder pollen is a minor factor.

Experiments with rats and mice have shown that modest initial doses of protein antigen, *e.g.* 10 µg to a rat, given together with an adjuvant, can elicit a boostable immunoglobulin E response (Jarrett, 1977; Katz, 1978). An optimum concentration of antigen can be determined. The present results suggest that a comparable situation may occur in the human neonate.

The microgram or nanogram quantities of pollen antigens, which reach the newborn infant during the first pollen season, can apparently initiate an immunoglobulin E response slow to develop and increase the risk of pollen allergy for a period of 20 years. The dose appears to be below the optimum, since the risk increases with an increasing quantity of pollen. On the other hand, there is some evidence to show that the risk of formation of cow's milk-specific IgE may in young children increase with decreasing dose (Björkstén & Saarinen, 1978; Kaplan & Solli, 1979). This may be due to the fact that the usual cumulated doses of milk-protein antigens are in the range of milligrams or grams and presumably above the optimum.

Additional studies of the early environmental factors which affect the development of immunoglobulin E mediated allergy should lead to useful suggestions for the prevention of the disease.

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