

Dependence of immediate hypersensitivity on the month of birth

F. BJÖRKSTÉN and I. SUONIEMI

Hospital for Allergic Diseases, Helsinki University Central Hospital, Helsinki, Finland

Summary

This report describes a retrospective study of 1421 patients allergic to pollens and 728 patients allergic to animal epithelia. In males, but not in females, the month-of-birth distribution differed significantly from that in the total population of Finland ($P < 0.01$ in pollen allergy and $P < 0.05$ in epithelium allergy). The phenomenon was most clearly apparent in boys aged 10–14 born in 1960–4 ($P < 0.01$ in pollen allergy and $P < 0.001$ in epithelium allergy). When the relative risk of immediate hypersensitivity was plotted as a function of the month of birth, a two-phasic curve with maxima in March–May and September–November was obtained for both pollen allergy and animal epithelium allergy. The results indicate that boys, but perhaps not girls, have a sensitive period early in life during which one or more environmental factor and seasonal variations in this factor influence the development of subsequent immediate hypersensitivity.

Introduction

The occurrence of immediate hypersensitivity (allergy of type I) (Gell & Coombs, 1968) is known to depend on both genetic and environmental factors. It has repeatedly been suggested that the newborn infant with his immature immune system might be particularly vulnerable to allergens in the environment. Accordingly, it has been observed that children receiving a diet low in allergenic foods during their first 6–9 months develop allergies later (Koivikko, 1974) or less frequently (Johnstone & Dutton, 1966) than others. On the other hand, it has also been speculated that early exposure to an allergen might confer immunological tolerance and prevent the development of immediate hypersensitivity (Reed, 1958).

Previously Björkstén & Johansson (1975) have observed that, on one hand animal epithelium allergies, and on the other hand birch and timothy pollen allergies tend to cluster, that is, occur together more often than expected. Clustering of pollen allergies could conceivably be explained by the seasonal occurrence of pollens and their effects on the neonate. This led us to study the dependence of pollen and animal epithelium allergies on the month of birth.

Patients and Methods*Patients*

We examined the hospital records of a group of 1 421 patients allergic to pollens and a group of 728 patients allergic to animal epithelia (Table 1). Less than fifty patients belonged to both groups. Patients' ages are given as at December 31, 1974.

In the pollen-allergy group we included all patients receiving hyposensitization therapy for one or more pollen allergies at this hospital during the last quarter of 1974.

Table 1. Number of patients by type of allergy, sex, age and month of birth

Type of allergy	Sex	Age (years)	Month of birth												All	P *
			1	2	3	4	5	6	7	8	9	10	11	12		
Pollen	Male	5-9	13	8	25	23	13	10	14	10	9	8	12	7	152	<0.05
		10-14	15	16	30	37	21	26	20	16	8	20	17	13	239	<0.01
		15-19	7	10	16	17	12	13	9	9	13	11	13	13	143	N.S.
		20-	23	19	33	16	37	28	19	21	28	18	20	13	275	<0.05
		All	58	53	104	93	83	77	62	56	58	57	62	46	809	<0.01
Pollen	Female	5-9	11	5	14	5	5	5	8	5	6	5	4	5	78	N.S.
		10-14	6	5	9	12	17	12	9	11	4	12	8	8	113	N.S.
		15-19	13	16	10	10	12	11	7	9	3	9	6	6	112	N.S.
		20-	22	26	30	27	32	21	28	18	28	28	27	22	309	N.S.
		All	52	52	63	54	66	49	52	43	41	54	45	41	612	N.S.
Epithelium	Male	5-9	3	6	4	11	7	5	2	9	10	7	9	7	80	N.S.
		10-14	10	2	11	7	18	5	1	3	13	11	8	3	92	<0.001
		15-19	4	4	7	6	8	4	5	7	9	3	2	4	63	N.S.
		20-	14	7	16	11	18	14	11	10	6	13	9	15	144	N.S.
		All	31	19	38	35	51	28	19	29	38	34	28	29	379	<0.05
Epithelium	Female	5-9	6	3	8	3	2	4	3	3	2	4	8	1	47	N.S.
		10-14	7	8	7	8	8	6	3	4	7	6	1	5	70	N.S.
		15-19	5	8	3	3	6	4	3	4	5	3	4	2	50	N.S.
		20-	23	9	16	18	17	24	14	10	21	10	9	11	182	N.S.
		All	41	28	34	32	33	38	23	21	35	23	22	19	349	N.S.

* The month-of-birth distribution in patient and corresponding reference population groups (obtained from the total Finnish population) were compared. The significance of differences is indicated by *P* values. N.S. = not significant ($P > 0.1$).

In the epithelium-allergy group we included all patients who had undergone intracutaneous skin testing during the period January, 1974 to July, 1975 and in whom a positive reaction to one or more mammalian epithelia (wool excluded) had been observed. Skin testing was performed with allergens in Coca's solution, with 100 mg/l histamine dihydrochloride in Coca's solution, and with Coca's solution alone. A skin reaction was regarded as positive when the area of the weal caused by the allergen was larger than that caused by Coca's solution alone and at least half as large as that caused by the histamine solution.

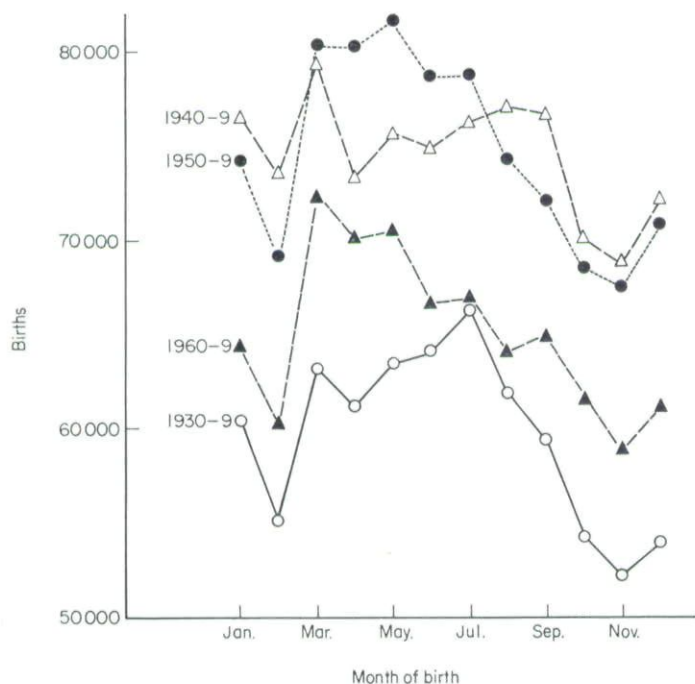


Fig. 1. Number of live births in Finland in various decades as a function of the month. ○—○ 1930-9; △---△, 1940-9; ●·····●, 1950-9; ▲---▲, 1960-9.

As a reference group we used the total population of Finland. Preliminary data on the total population by sex and 5-year age groups at the end of 1974 was available (Tilastotiedotus VÄ, 1975). The month-of-birth distributions in these groups were assumed to be identical with those found in monthly birth records for the corresponding groups in the period 1930-69 (Fig. 1) (Official Statistics of Finland, 1930-69). For those born before 1930 the month-of-birth distribution was assumed to be identical with that in the period 1930-9. The total population numbered 4,692,614.

Statistical methods

The month-of-birth distribution in all men and all women allergic to pollens was compared with the distribution in the entire population of the country after adjustment for sex and age. A χ^2 test was used to test the significance of differences (Rao, 1973). Age adjustment was carried out using 5-year age groups in the age span 5-34, and the age groups 34-45 and 45 and above. Age adjustment did not affect the probabilities obtained, and age adjustment was omitted when other population groups comprising all ages were treated.

The relative risk of developing an allergy for those born in month j was estimated using the equation

$$R_j = \frac{n_j}{n p_j}$$

where R_j is the relative risk, n_j is the number of patients born in month j , n is the total number of patients and p_j is the multinomial probability for birth in month j . The

product $n p_j$ can also be characterized as the estimated number of patients had the patients' month-of birth distribution been identical with that in the total population of the country (after adjustment for sex and age where applicable). To test whether the relative risk for a particular month j is different from 1, is equivalent to testing whether there is a departure from the multinomial distribution of the null hypothesis in the particular month cell j . Here the test is based on the statistic

$$\frac{n_j - n p_j}{(n [1 - p_j] p_j)^{0.5}}$$

which is asymptotically normal with mean 0 and variance 1 (Rao, 1973).

Results

In both the pollen-allergy and the epithelium-allergy group there were significantly more males than expected from the total Finnish population after age adjustment ($P < 0.001$ and $P < 0.05$ respectively).

Both in male patients allergic to pollens and allergic to epithelia the month-of-birth distribution differed significantly from that in the proper reference population group (obtained from the total Finnish population). This was true for all males and also for several age groups. The phenomenon was best discernible in boys aged 10–14 (born in 1960–4) (Table 1). When all males were divided into subgroups according to the allergen involved, the month-of-birth distribution in several subgroups was again significantly different from that in the reference group (Table 2).

In females the relative risk of developing immediate hypersensitivity tended to vary with the month of birth in a manner similar to that observed in men (Fig. 2). In no female group, however, did we find a month-of-birth distribution significantly different from that in the reference population. This was true both for the age groups listed in Table 1 and for additional groups aged 5–14, which were tested.

The effect of the season of birth on the risk of subsequent hypersensitivity can be

Table 2. Number of male patients by allergy and month of birth

Allergy	Month of birth												All	P *
	1	2	3	4	5	6	7	8	9	10	11	12		
Tree (<i>Betulaceae</i>) pollen	38	37	58	51	51	44	39	33	32	32	40	25	480	<0.1
Grass (<i>Gramineae</i>) pollen	36	36	74	76	69	59	43	37	39	45	46	33	593	<0.001
Mugwort (<i>Artemisia vulgaris</i>) pollen	15	12	29	22	18	24	20	14	23	13	14	14	218	N.S.
Other pollen	8	6	17	12	17	15	14	13	8	6	12	4	132	N.S.
Cow epithelium	12	5	14	10	18	12	5	7	15	14	10	16	138	<0.1
Horse epithelium	17	9	18	16	23	13	11	12	19	20	14	17	189	N.S.
Small mammal (cat, dog, guinea-pig, hamster) epithelium	12	8	20	25	28	15	8	18	20	15	19	13	201	<0.05

* The month-of-birth distribution in patient and corresponding reference population groups (obtained from the total Finnish population) were compared. The significance of differences is indicated by P values. N.S. = not significant ($P > 0.1$).

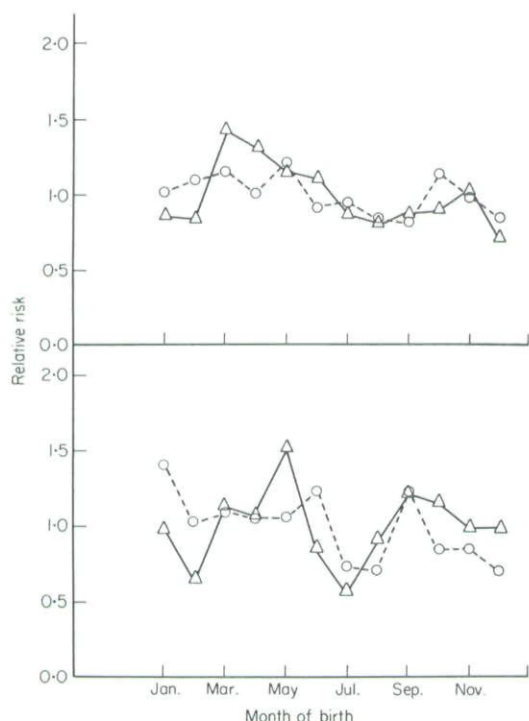


Fig. 2. Relative risk of pollen allergy (top graph) and animal epithelium allergy (bottom graph) in males and females as a function of the month of birth. By definition, the relative risk is 1 in a total patient group such as all females allergic to a pollen. Δ — Δ , Males; $\circ$ — $\circ$, females.

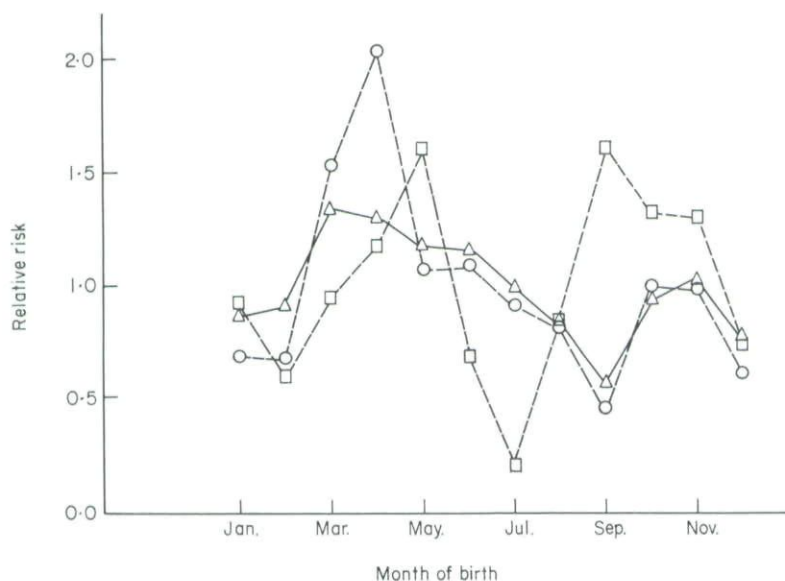


Fig. 3. Relative risk of grass (*Gramineae*) pollen allergy ($\circ$ — $\circ$), tree (*Betulaceae*) pollen allergy (Δ — Δ) and animal epithelium allergy ($\square$ — $\square$) as a function of the month of birth in boys aged 5-14 (born in 1960-9). By definition, the relative risk is 1 in a total patient group such as all boys allergic to a grass pollen.

illustrated most clearly for boys aged 5–14 (born in 1960–9) (Fig. 3). When the relative risk is plotted as a function of the month of birth a two-phasic curve is obtained. The risk is relatively high for those born in March–May and October–November (also for those born in September in the case of animal epithelium allergy), and lower for those born between these periods.

Variations in relative risk between month-of-birth groups were considerable. For example, in boys aged 5–14 and allergic to a grass pollen, relative risks were in the range 0.45 (September) to 2.03 (April). These risks were significantly different from 1 ($P < 0.01$ and $P < 0.001$ respectively). Even larger relative differences were observed in those allergic to an animal epithelium (Fig. 3).

Relative risk *v.* month of birth curves for tree pollen and grass pollen allergy were quite similar, while the curve for epithelium allergy differed somewhat. Differences included displacement of maxima and minima by a month or two and a different relative-risk level in the autumn (Fig. 3).

Discussion

Our patient population groups contained persons suffering from immediate hypersensitivity (allergy of type I). Due to diagnostic difficulties and deficiencies some non-allergic persons may have been included. This is particularly true in the case of animal epithelium allergy, where skin testing alone was used as a selection criterion. The deficiencies in patient selection should tend to obscure any true differences between month-of-birth groups or other groups. As a consequence, the present statistics should be considered as conservative estimates.

Immediate hypersensitivity predominantly affects children and young adults. Several studies have shown that it occurs earlier in boys than in girls (Koivikko, 1974; Blair, 1974; Broder *et al.*, 1974a, b). Thus it is not surprising that there were many children and many males among the patients (Table 1).

When we grouped the male pollen-allergy patients by the month of birth, we found a significantly increased relative risk of disease in those born in the spring. The risk was lowest in those born in the summer and the winter (Figs 2 and 3). Such variations in risk with the season of birth must be related to seasonal variations in some factor affecting children early in life. We interpret the observation as proving the existence of an early sensitive period during which an environmental factor or factors can influence the occurrence of subsequent immediate hypersensitivity.

After the pollen-allergy part of the study it seemed possible that the seasonal factor could be identical with the environmental pollen concentration. We proceeded to study animal epithelium allergy assuming that seasonal variations in allergen concentration would be negligible and that no dependence of risk on the month of birth would be found. Contrary to expectations, however, we did find a dependence, which was similar to that in pollen allergy or even somewhat more profound (Figs 2 and 3). The observation was again significant only in males, although a similar trend could be seen among females.

Apparently there is an important seasonal factor or factors other than the allergen concentration. It is possible, however, that seasonal variations in the pollen concentration causes an additional effect. Such an effect is suggested by the fact that the relative risk of pollen allergy and epithelium allergy do not vary with the month of birth in an identical manner (Fig. 3).

Whether the seasonal factor or factors tends to protect or predispose the infant

to future immediate hypersensitivity cannot be determined from the present results. The sensitive age at which the factor is active or maximally active also remains uncertain. A period during the first year of life would seem probable, but a somewhat later period or a fetal period cannot be ruled out. Males are certainly affected by the factor, but for females the situation is uncertain. The phenomenon we describe is most distinct in boys aged 10–14 born in 1960–4. This raises the question whether the age or the year of birth could be of importance.

Identification of the seasonal factor poses problems. Finland is located at a high latitude (between 60° and 70° north), and the length of day, weather conditions, infection incidencies, diet and also other possible factors undergo considerable seasonal variations. These large variations in Finland could perhaps explain why the month-of-birth effect is so clearly evident in the present data. In similar previous studies no significant dependence of pollen allergy on the season of birth could be observed (Reed, 1958; Smith, 1970; Kleiner, Arkins & Lauwasser, 1975). These negative results may also be due to the small number of patients examined or an unfavorable sex and age distribution.

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