

ORIGINAL PAPER

Sensitization to different pollens and allergic disease in 4-year-old Swedish children

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Clinical and
Experimental
Allergy

Summary

Background Although the relationship between sensitization to different inhalant allergens in adolescents and adults has been intensively studied, information concerning sensitization in children is scarce in particular to pollens.

Objectives In 4-year-old children to elucidate the pollen immunoglobulin (IgE) antibody profile (birch only, timothy only and combinations of three pollens (birch, timothy or mugwort) and to relate the results to other inhalant and food allergens, as well as the presence of allergic diseases.

Methods A total of 2551 4-year-old children belonging to a prospective birth cohort, which has been followed longitudinally (BAMSE), were investigated with respect to IgE antibodies to pollen and other inhalant and food allergens, and expression of allergic disease, based on questionnaire data.

Results Eleven percent ($n = 285$) of the children were sensitized to pollen. Birch was the dominating cause of pollen sensitization (birch sensitization only, $n = 133$); followed by timothy grass pollen ($n = 56$) and a combination of two ($n = 64$) or three ($n = 30$) pollens. A remarkably high proportion of the children sensitized only to birch was also sensitized to other inhalant allergens. This was not seen for children sensitized only to timothy. The highest frequencies of IgE reactivity to food were found in the group of children sensitized to the combination of birch, timothy and mugwort pollen. Children sensitized to timothy only, exhibited symptoms of allergic disease significantly less frequently compared with children sensitized to birch only. Sensitization to birch pollen was found to be closely associated with rhinitis and eczema compared with asthma. The highest frequency of asthma and/or rhinitis and/or eczema was reported in children sensitized to at least two pollens.

Conclusion Our results demonstrate that birch is the dominating source of pollen sensitization at the age of four in Sweden. This might associate with the pattern of sensitization to other inhalant and food allergens as well as influence on the expression of allergic disease in this particular age group.

Keywords allergic disease, BAMSE, childhood, food allergen, IgE antibody, inhalant allergen, sensitization

Submitted 5 August 2005; revised 16 December 2005; accepted 27 January 2006

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Introduction

In many western countries around 15–20% of pre-school children are sensitized to inhalant allergens before the age of seven [1]. These children are at risk of developing asthma which may persist throughout adult life [1]. The

most common inhalant allergens affecting young children in Sweden are birch (9%), cat (6%), timothy (6%) and horse (5%) [2]. Although many studies have pointed out an association between sensitization to inhalant allergens and certain food allergens [3–6], this has attracted little attention in childhood.

Sensitization to food allergens frequently precedes development of inhalant allergy [1, 3–8]. The most prevalent triggers of food allergy in children under the age of two are egg and milk [9, 10]. From the third birthday on, the prevalence of immunoglobulin (Ig)E antibodies to inhalant allergens, for instance birch and grass pollen, has been shown to rise significantly, subsequently overtaking the sensitization to food allergens [7].

Recently, exposure to high levels of birch pollen during pregnancy and early infancy has been proposed to result in an increased probability of sensitization to the same allergens and symptoms of atopic disease at 5 years of age [11, 12]. Among pre-school children in Scandinavia information regarding sensitization to grass, like timothy, in relation to allergic disease is to our knowledge unknown.

The aim of the present study was to elucidate the pollen IgE antibody profile and to relate the results to sensitization to other common inhalant and food allergens as well as the presence of allergic diseases in a prospective birth cohort of 4-year-old children.

Methods

Study subjects

Subjects in this study were selected from the ongoing BAMSE study, which has a prospective longitudinal birth cohort design to assess risk factors for asthma and other allergic diseases in early childhood [13]. Details about the BAMSE study have been published elsewhere [13–16]. Briefly, a total of 4089 unselected newborns were recruited during 1994–1996. Data on background factors such as allergic heredity and parental smoking were requested from the parents when the child was 2 months old (median age). When the children were 1 and 2 years old, similar questionnaires were mailed to all parents, requesting information on breastfeeding, parental smoking and allergic symptoms, including airway reaction to pollen and pets. At 4 years, new questionnaires on symptoms were distributed to all parents. The response rates for the questionnaires at 1, 2 and 4 years of age were 96, 94 and 91%, respectively. At 4 years of age, venous blood samples were obtained from 2614 children. Data on key variables such as exposure and outcome had to be complete for the individual to be included in the study, leaving 2551 children in the whole study group.

Determination of specific IgE antibodies to inhalant and food allergens

In the first step all sera were screened with Phadiatop[®] (a mixture of inhalant allergens: birch pollen (*Betula verrucosa*), timothy grass pollen (*Phleum pratense*), mugwort pollen (*Artemisia vulgaris*), house dust mite (*Dermatophagoides pteronyssinus*), mould (*Cladosporium herbarum*),

cat, dog and horse dander) (Pharmacia Diagnostics AB, Uppsala, Sweden) and the multi-allergen food test fx5[®] (a mixture of food allergens: egg white, cow's milk, fish, wheat, peanut and soybean allergens) (Pharmacia Diagnostics AB, Uppsala, Sweden) according to the instructions of the manufacturer (UniCAP, Pharmacia Diagnostics AB). In the second step, sera scoring positive in Phadiatop and/or fx5 were further analysed to determine reactivity to each individual allergen. Sensitization was defined as a positive ImmunoCAP (≥ 0.35 kU_A/L).

Definition of allergic diseases

Heredity for allergic disease was defined as doctors-diagnosed asthma and/or hayfever in combination with allergy to furred pets or pollens in any (mother, father or both) or no parent [2, 15, 16]. Questions on wheezing were slightly modified from ISAAC questionnaires [17]. Asthma at 4 years of age was defined as > 3 episodes of wheezing over the last year, or > 1 episode if the child had been given inhaled steroids. Rhinitis was defined according to the ISAAC criteria: sneezing, runny or blocked nose without common cold more than once in the last 12 months. Eczema denoted reports of dry skin and itchy rash on specific locations more than once in the last 12 months or that the child had a doctor's diagnosis of eczema at 4 years [18]. Pollen sensitization at the age of four was defined as having IgE antibodies to one or more of the three pollen allergens tested (birch, timothy grass and mugwort).

Statistical methods

Prevalence figures are given in total numbers and in percent. Differences in prevalence between children with no heredity and any heredity, except pollen, as well as between children with no heredity and heredity, only pollen and between gender (Table 1) were investigated using a χ^2 approximation of the exact binomial test. In those cases where the χ^2 assumption was too weak, an exact binomial test was performed. Differences between children with no disease and any allergic disease, as well as between children sensitized to timothy only and other pollen groups with respect to disease (Table 2) were also investigated using a χ^2 approximation or the exact binomial test. Allergen-specific IgE antibody levels were estimated as geometric means. Differences in IgE levels between pollen groups were tested using the Wilcoxon test. A *P*-value < 0.05 was considered as significant. All major analyses were performed using SAS V8.2.

Ethical considerations

The Ethics Committee of the Karolinska Institute (Stockholm, Sweden) approved the study. The parents of all participating children gave their informed consent.

Table 1. Distribution of background factors among children 4 years of age in the BAMSE cohort subdivided by no sensitization or sensitization (≥ 0.35 kAU/L) to timothy or birch pollen only or two pollens or more

	Total N = 2551		No sensitization N = 1937		Timothy only N = 56		Birch only N = 133		Two pollen or more N = 94	
	n	%	n	%	n	%	n	%	n	%
No heredity	832	33	674	35	10	18	30	23	19	20
Any heredity, except pollen	712	28*	539	28*	15	27	39	29	16	17
Heredity, only pollen	1007	39 [†]	724	37	31	55 [†]	64	48 [†]	59	63 [†]
Gender, male	1294	51	951	49	29	52	79	59 [‡]	63	67 [‡]
Gender, female	1257	49	986	51	27	48	54	41	31	33

*Comparison between children with no heredity and any heredity, except pollen ($P < 0.05$).

[†]Comparison between children with no heredity and heredity, only pollen ($P < 0.05$).

[‡]Comparisons between gender ($P < 0.05$).

Results

Sensitization profile to pollen allergens

The whole study population comprised 2551 4-year-old children, of whom 614 (24.1%) were sensitized and had a positive Phadiatop and/or fx5. Of these, 285 (11.2%) had IgE antibodies to pollen (birch and/or timothy and/or mugwort) and were selected for further investigation (pollen group).

The 285 pollen-sensitized children were characterized according to their IgE antibody reactivity to a particular pollen or pollen group (birch only, timothy only, two pollens and three pollens). One hundred thirty-three children were sensitized to birch as the only pollen; 56 to timothy as the only pollen, and 94 to a combination of two ($n = 64$) or three ($n = 30$) pollens (Table 1). Two children had IgE antibodies to mugwort alone (not shown). The children could in addition be sensitized to non-pollen allergens. The three groups of pollen sensitized children (birch pollen only, timothy only and at least two of three pollens – birch, grass or mugwort) were used for further analysis.

A history of parental pollen allergy was significantly more prevalent in the pollen groups compared with those without sensitization (Table 1). For birch and for two pollens or more, a significantly higher proportion of boys compared with girls were sensitized to pollen ($P < 0.05$).

Prevalence of IgE reactivity to animal dander and mould among pollen sensitized children

Children sensitized only to birch compared with those sensitized only to timothy demonstrated nearly a three times higher frequency of IgE reactivity to cat, horse and mould ($P < 0.05$) and a doubling to dog ($P < 0.05$) (Fig. 1). Among children sensitized to two or three pollens a significantly higher frequency of sensitization to cat and dog was observed compared with those sensitized only to timothy pollen ($P < 0.05$). Thus, there was a higher frequency of sensitization to cat and dog with sensitization to an increasing number of the pollens tested (Fig. 1). The geometric mean IgE levels for the different allergens were compared between the various pollen groups, showing an overall significant difference between the groups

Table 2. No disease, any disease, asthma, rhinitis and eczema at 4 years of age among different groups of pollen sensitized children

	Total N = 2551		Any of birch, timothy or mugwort N = 285		Timothy only N = 56		Birch only N = 133		Two pollen N = 64		Three pollen N = 30	
	n		n	%	n	%	n	%	n	%	n	%
No disease	1832		109	38	35	63	53	40	15	23	6	20
Any disease	719		176	62*	21	37*	80	60*	49	77 ^a	24	80 ^a
Asthma([†])	191		48	17	4	7	21	16 [†]	12	19 [†]	11	37 [†]
Rhinitis([§])	280		112	39	7	13	49	37 [†]	35	55 [†]	20	67 [†]
Eczema()	421		102	36	12	21	44	33 [†]	32	50 [†]	13	43 [†]

*Comparison between children with no disease and any disease ($P < 0.05$).

[†]Comparison between children sensitized to timothy only and the other pollen groups ($P < 0.05$).

[‡]This group can include children with rhinitis and or eczema.

[§]This group can include children with asthma and or eczema.

^{||} This group can include children with asthma and or rhinitis.

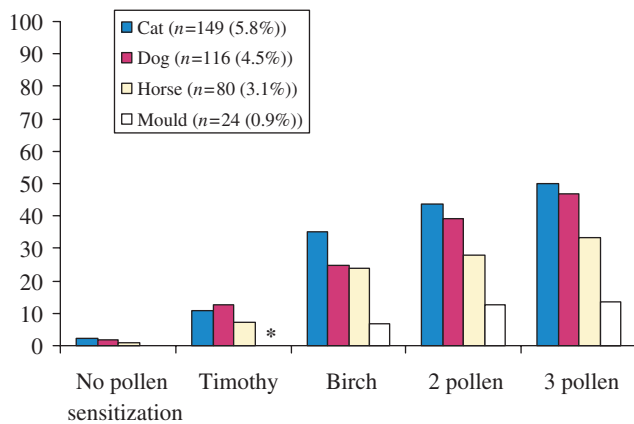


Fig. 1. Proportion of 4-year-old children sensitized to furred animals and mould, subdivided by pollen sensitization ($n=285$) and those without pollen sensitization ($n=1937$). The number of positive immunoglobulin E antibody results in the whole population is given for each allergen. There is a significant difference between birch and cat for all allergens ($P < 0.05$). *No sensitization to mould.

($P < 0.05$). For the two or three pollen group, allergen-specific IgE levels to animal dander were significantly ($P < 0.05$) higher than in the timothy group.

Prevalence of IgE reactivity to food allergens among pollen sensitized children

Children in the four major pollen groups were compared with respect to prevalence of IgE antibody reactivity to food allergens introduced early in life (egg white, milk, wheat) and food introduced later (peanut). Children sensitized only to birch or only to timothy demonstrated similar frequencies of IgE reactivity to milk, egg, wheat and peanut allergen. The highest frequencies of IgE reactivity to food were seen in children sensitized to all three pollens (birch, timothy and mugwort) compared with the other pollen groups ($P < 0.05$) (Fig. 2), which in particular was seen for peanut. For peanut, the frequency of IgE reactivity was 90% in children sensitized to birch, timothy and mugwort pollen compared with 44% in those sensitized to both birch and timothy pollen, and 19% and 14% in children sensitised to only birch or only timothy, respectively.

Allergic disease in relation to pollen sensitization

Of the 2551 children studied, 719 (28%) reported some form of allergic disease (asthma and/or rhinitis and/or eczema) (Table 2). Among the 285 pollen-sensitized children, 176 (62%) displayed one or more of these diseases. The highest frequency of asthma and/or rhinitis and/or eczema was reported in children sensitized to two (77%) or three (80%) pollens.

Children sensitized only to timothy exhibited a significantly lower frequency of symptoms of allergic disease

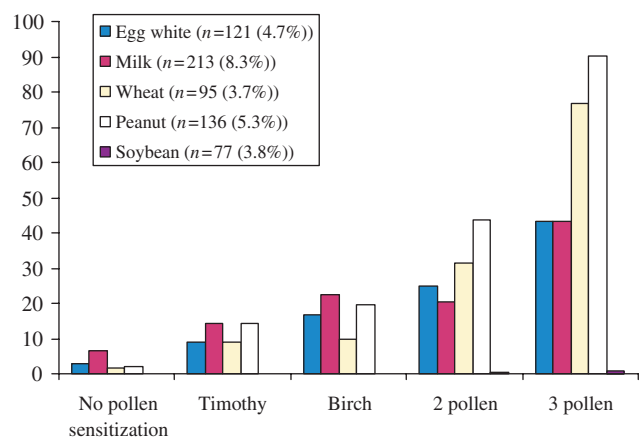


Fig. 2. Proportion of 4-year-old children sensitized to food allergens, subdivided by pollen sensitization ($n=285$) and those without pollen sensitization ($n=1937$). The number of positive immunoglobulin E antibody results in the whole population is given for each food allergen. There was a significant difference between the three pollen group and the pollen groups ($P < 0.05$). *No sensitization to mould.

compared with children sensitized only to birch or to any combination including birch (37% vs. 60%; 77%; and 80%, respectively) (Table 2). Sensitization only to birch pollen was found to be closer associated with rhinitis compared with sensitization to timothy only. Asthma as symptoms in relation to any pollen sensitization was less frequent than eczema and rhinitis.

Discussion

We have investigated whether there is an association between sensitization to pollen and other inhalant and food allergens as well as expression of allergic diseases in 4-year-old children from Stockholm, Sweden. The study was based on a population-based birth cohort of children who have been followed longitudinally (BAMSE). Our main finding is that among children as young as 4 years of age, birch is the dominating cause of pollen sensitization. This seems to be associated with sensitization to other inhalant allergens as well as expression of allergic disease. The results probably reflect the high levels of birch pollen exposure in Scandinavia: the birch pollen counts in Stockholm during the last 15 years have been shown to be seven times higher than the grass pollen counts [19]. Our data in 4-year-old children are in agreement with a recent study demonstrating that the profile of IgE reactivity to birch pollen allergens in adults may differ between European populations because of differences in pollen exposure [20]. Furthermore, sensitivity to the major birch pollen allergen Bet v 1 was shown to be dominating in Swedish subjects but not in subjects from Switzerland or Italy [20]. Therefore, taking all this information into account, the pollen reactivity profile seen in adults in Scandinavia seems to be established already in childhood.

We observed a remarkably high proportion of cat-sensitized children in the birch pollen group compared with the timothy pollen group. Cat sensitization was also dominating in the other three groups where birch pollen sensitization was observed. Because the results demonstrate that sensitization to timothy was not associated with that of cat it seems that the allergen most potent in driving IgE sensitization in Scandinavia may be birch pollen. Furthermore, it has recently been shown that a short high-dose exposure, as during a pollen season, might result in risk of sensitization [11].

We found that children in the pollen groups that included birch pollen demonstrated a higher prevalence of allergic diseases compared with children sensitized to timothy pollen. The proportion reporting each specific allergic disease was significantly higher among children sensitized to birch compared with those sensitized only to timothy grass pollen.

The children included in this study were only 4 years old. It could be argued that it is too early to investigate the influence of pollen sensitization on sensitization to inhalants and food, because a number of children will develop sensitization to pollen allergens the coming years. On the other hand, a tendency toward earlier sensitization and development of allergic disease has been noted during recent years [21]. Thus we feel it is relevant to examine these phenomena even in children this young.

This is the first study to investigate the association between sensitization to pollen and other inhalants and food allergens in such a young population. The findings are of particular interest, because pollen allergens are ubiquitous in the environment and may affect pre-disposed children regardless of any possible attempts to avoid exposure. Our results demonstrate that birch pollen is the dominating source of pollen sensitization already at the age of four in Sweden. This seems to associate with the sensitization pattern to other inhalant and food allergens as well as expression of allergic disease in this age group.

Acknowledgements

The investigation was supported by grants from the Center for Allergy Research at Karolinska Institutet, the Swedish Research Council, the Vårdal Foundation for Health Care Sciences and Allergy Research, the Swedish Asthma and Allergy Association, the Swedish Heart-Lung Foundation, the Hesselman Foundation, the King Gustaf V 80th Birthday Foundation, the Swedish Cancer and Allergy Fund, and the Karolinska Institutet.

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