



ORIGINAL ARTICLE

Patterns of sensitisation to common food and inhalant allergens and allergic symptoms in pre-school children

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Aim: Sensitisation to allergens and allergy symptoms depends on age, but this relationship is poorly understood. We therefore investigated the effect of age on allergen sensitisation and allergy symptoms in pre-school children.

Methods: A cross-sectional study was conducted on 629 Korean children (age 3 to 6 years). Current allergic symptoms were assessed by the Korean version of the International Study of Asthma and Allergies in Childhood questionnaire that was adapted for pre-school children. Sensitisation to five airborne and three food allergens was evaluated by a skin prick test. χ^2 test was used to analyse differences in age trend. Multiple logistic regression analysis was performed to obtain the adjusted odds ratios (aOR) for allergic disease.

Results: As age increased, the prevalence of current rhinitis ($P < 0.001$), the sensitisation to pollen allergens ($P < 0.001$) and polysensitised children ($P = 0.002$) increased, but the prevalence of current asthma ($P = 0.010$) and the sensitisation to food allergens ($P = 0.009$) decreased. There was no effect of age on the prevalence of current eczema ($P = 0.685$), monosensitised children ($P = 0.282$) and atopy ($P = 0.160$). The agreement between sensitisation to dust mites and atopy increased with age, and was 93% at age 6 years ($P = 0.05$). The polysensitisation (aOR = 3.0 (95% CI, 1.4–5.0), $P < 0.005$) and the presence of eczema in the first 2 years of life (aOR = 4.1 (95% CI, 2.2–7.6), $P < 0.001$) were significant independent risk factors for current rhinoconjunctivitis.

Conclusion: The type and number of allergen sensitisations and allergic symptoms changed from age 3 to 6 years. Careful follow-up of changes in sensitisation patterns may provide a better understanding of the pathogenesis of the allergic march.

Key words: allergen; allergic march; polysensitisation.

What is already known on this topic

- 1 Allergen sensitisation is associated with allergic diseases in children, changing dynamically with age.
- 2 Polysensitisation is associated with more severe atopic diseases.
- 3 The relationship between sensitisation and allergic diseases in pre-school children is poorly understood.

What this paper adds

- 1 Sensitisation to dust mite at an early age may be a predictor for the development of aero- and polysensitisation in children aged 6 years and older.
- 2 Polysensitisation was a significant independent risk factor for current rhinoconjunctivitis.
- 3 Allergic symptoms and sensitisation patterns change significantly by the age of 4 years, and these factors significantly impact each other.

Sensitisation to allergen has long been known to relate to childhood allergic disease and has been shown to be associated with the development of subsequent childhood atopic disease.^{1,2} Therefore, early detection of specific immunoglobulin E antibodies to allergens could facilitate allergy prevention in

children.² Sensitisation to allergen is associated with the start of the allergic march, which is characterised by the progression from atopic dermatitis to allergic rhinitis during the first several years of life.³

The prevalence of allergic disease depends on patient age,⁴ gender,⁵ Western life-style,⁶ second-hand smoking,⁷ nutrition,⁸ location^{9,10} and pollution.¹¹ Among these factors, changes in sensitisation pattern^{12–14} are considered to be an important factor in children.¹⁵ The association between allergic symptom and sensitisation to allergen is known to be complex, changing dynamically with age.^{14,16–18} Food allergens are associated with atopic dermatitis,¹ whereas inhalant allergens are associated with allergic rhinitis and/or asthma.¹⁵ Recent studies revealed that polysensitised individuals have more severe atopic disease,^{1,19} and specific allergens such as birch pollen⁶ or house dust

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Conflict of interest: No author has a financial conflict of interest with regard to the material presented in this paper.

Institute at which the work was performed: CHA University School of Medicine.

Accepted for publication 9 October 2012.

mite¹² are linked to specific diseases. However, little is known about the mechanism underlying the allergic march with regard to the prevalence of sensitisation to common allergens, in particular the atopic sensitisation of pre-school children.

In the present study, we performed skin testing to evaluate sensitisation to common food and inhalant allergens and investigated the prevalence of allergic diseases in pre-school children by use of the standard International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. We hypothesised that the type and number of sensitisations in pre-school children would change with age and that this age-related change might be associated with changes in allergic symptoms or disease.

Methods

Study population

The study population ($n = 629$) consisted of children randomly selected from six day care centres in Seongnam, Korea, between April 2009 and June 2009 whose parents answered the Korean version of the ISAAC questionnaire. The parents of 613 children (97.4%) returned completed questionnaires, and skin prick testing was performed on 534 children. The CHA University ethics committee approved this study, and the parents of all participating children provided written informed consent.

Questionnaire

The expanded ISAAC questionnaire¹⁰ was in two parts, which comprised questions posed to parents relating to the prevalence of eczema, rhinitis and asthma in their children; the information requested included the following: (i) parental reports of symptoms of allergic diseases; (ii) parental reports of current symptoms of allergic disorders; (iii) parental reports of treatment of allergic disease; and (iv) parental reports of diagnosed allergic diseases. An additional question about onset of eczema was utilised in our survey. Parents were asked whether their child had newly developed eczema before 2 years of age or after 2 years, on the condition that the children had eczematous rashes in the past 12 months. The second part of the questionnaire contained questions relevant to possible environmental risk factors for the development of these conditions. These environmental questions were regarding parental allergies and the presence of cigarette smoker(s) and pets in the household.

Based on the modified diagnostic criteria,⁴ we classified a child as having current asthma if there was a positive answer to the written question 'Has your child had wheezing or whistling in the chest in the past 12 months?' We classified a child as having current rhinitis if there was a positive response to the question 'In the past 12 months, has your child had a problem with sneezing or a runny or blocked nose when you (he/she) did not have a cold or the flu?' We classified a child as having current rhinoconjunctivitis if there was a positive response to the question 'In the past 12 months, has this nose problem been accompanied by itchy watery eyes?' We classified a child as having current eczema if there were positive answers to two questions: 'Has your child had this itchy rash at any time in the past 12 months?' and 'Has this itchy rash at any time affected any of the following places: the folds of the elbows; behind the

knees; in front of the ankles; under the buttocks; or around the neck, ears, or eyes?' These questions were preceded by the question 'Has your child ever had a recurring skin rash of at least 6 months' duration?'

Skin prick test

Skin prick tests were performed with extracts of three common food allergens (milk, egg and peanut) and five common aero-allergens (*Dermatophagoides pteronyssinus*, cat dander, birch pollen, ragweed, mixed mould) produced by Allergopharma (Reinbeck, Germany). These allergens were selected based on a report that identified common allergens in our geographical area.²⁰ A positive skin reaction was defined as a wheal that was 3 mm or greater in diameter, after subtraction of the negative control. Atopy was defined as presence of at least one positive skin prick test reaction. Sensitisation to only one allergen was defined as monosensitisation, and sensitisation to two or more allergens was defined as polysensitisation.

Statistical analysis

All data were analysed with Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) for Windows, version 11.0. χ^2 tests were used to compare categorical items and changes in current asthma, current rhinitis and current eczema by use of linear-by-linear association. Differences in specific allergen sensitivities to food, inhalants and mixed allergens were assessed by the Wilcoxon rank sum test. Multiple logistic regression models were used to identify variables that were independently associated with sensitisation and environmental factors. All results are expressed as odds ratios (ORs) with 95% confidence intervals (95% CI). The level of significance was set at 5%.

Results

Basic characteristics of atopic and non-atopic children

Table 1 shows the basic characteristics of the 534 pre-school children for whom questionnaires and skin prick test results were available. Overall, 131 children (24.5%) were sensitised to at least one allergen (skin test positive).

Table 1 Demographic characteristics of enrolled children ($n = 534$)

Age, months $\pm$ SD	59.9 $\pm$ 10.7
Male, n (%)	287 (53.7)
Parental history of asthma†, n (%)	41 (7.7)
Maternal history, n (%)	26 (4.9)
Paternal history, n (%)	16 (3.0)
Secondary smoking, n (%)	206 (38.6)
Children with pets in household, n (%)	19 (3.6)
Prematurity or low birthweight, n (%)	19 (3.6)
Skin test positive, n (%)	131 (24.5)

†Parental asthma was defined as presence of asthma in mother or father.

Table 2 Prevalence rates of allergic symptoms and atopic sensitisation

	Non-atopy (<i>n</i> = 403)	Atopy† (<i>n</i> = 131)	<i>P</i> -value
Male, <i>n</i> (%)	210 (52.1)	77 (58.8)	0.184
Age, months ± SD	59.6 ± 10.5	60.9 ± 11.3	0.219
Current asthma, <i>n</i> (%)	47 (11.7)	25 (19.1)	0.031
Current rhinitis, <i>n</i> (%)	149 (37.0)	67 (51.1)	0.004
Current eczema, <i>n</i> (%)	57 (14.1)	36 (27.5)	<0.001
Secondary smoking, <i>n</i> (%)	218 (54.1)	58 (44.3)	0.051
Pets, <i>n</i> (%)	13 (3.2)	6 (4.6)	0.467
Parental asthma, <i>n</i> (%)	31 (7.7)	10 (7.6)	0.983
Prematurity or low birthweight, <i>n</i> (%)	13 (3.2)	6 (4.6)	0.467

†Atopy was defined as presence of at least one positive skin prick test reaction.

Table 3 Characteristics of sensitisation for different age groups

	3 years (<i>n</i> = 83)	4 years (<i>n</i> = 164)	5 years (<i>n</i> = 202)	6 years (<i>n</i> = 85)	<i>P</i> -value
Atopy†, %	27 (17–36)	19 (12–24)	25 (19–31)	33 (23–43)	0.160
Der p, %	17 (9–25)	15 (10–21)	22 (16–28)	31 (21–41)	0.008
Food Allergen, %	10 (3–16)	2 (0–4)	2 (0–3)	2 (0–6)	0.009
Pollen Allergen, %	4 (0–8)	7 (3–11)	11 (7–16)	21 (12–30)	<0.001
Monosensitisation, %	18 (10–27)	13 (8–18)	14 (10–19)	11 (4–17)	0.282
Polysensitisation, %	8 (2–15)	6 (2–10)	10 (6–15)	22 (13–31)	0.002
Der p, PPA‡	63	80	88	93	0.005

Data are presented as percentage (95% confidence interval). Significant *P*-values (*P* < 0.05) are in bold.

†Atopy was defined as presence of at least one positive skin prick test reaction. ‡Der p, PPA, positive predictive agreement between Der p positivity and atopy, obtained by linear-by-linear association with a χ^2 test.

Table 2 compares the characteristics of atopic and non-atopic children. Current symptoms (asthma, rhinitis and eczema) are more common in those that are atopic compared with those that are not. Other clinical and demographic characteristics were not significantly different between the atopic and non-atopic groups.

Prevalence of allergic diseases in children of different ages

The prevalence of current asthma decreased significantly with increasing age, from 20.5% (95% CI, 12–29%) at 3 years to 8.2% (95% CI, 2–14%) at 6 years (*P* = 0.010). In contrast, the prevalence of current rhinitis increased with increasing age, from 39.1% (95% CI, 28–49%) at 3 years to 61.0% (95% CI, 51–71%) at 6 years (*P* < 0.001). There were no significant age-related changes in the prevalence of current rhinoconjunctivitis (21.7% (95% CI, 13–31%) at 3 years to 21.2% (95% CI, 12–30%) at 6 years, *P* = 0.480) or current eczema (16.9% (95% CI, 9–25%) at 3 years to 15.3% (95% CI, 8–23%) at 6 years, *P* = 0.685). Among 93 subjects with current eczema, the percentages of subjects with onset of eczema before age 2 were 85.7% at 3 years, 45.2% at 4 years, 34.3% at 5 years and 46.2% at 6 years, whereas the percentages of newly diagnosed eczema after 2 years in those with current eczema were 14.3% (95% CI,

7–35%) at 3 years and 53.8% (95% CI, 23–85%) at 6 years (*P* = 0.020). As the children with current eczema age, the prevalence of newly diagnosed eczema after 2 years increases. These results indicate that the plateau in rates of eczema between 3 and 6 years reflects cases of newly diagnosed eczema after age 2.

Differences in sensitisation patterns in different age groups

Table 3 shows sensitisation rates to each allergen group for children in four age groups. In 3-year-old children, dust mites (17%) and food (10%) were the most common sensitisers, and pollen (4%) was the least common sensitiser. Pollen became a more common sensitiser as children became older (*P* < 0.001), whereas sensitisation to food allergens decreased with age (*P* = 0.009). The overall prevalence of atopy was similar for all age groups (*P* = 0.160).

Among 131 atopic subjects, 74 children (56%) were sensitised to one allergen (monosensitised group) and 57 children (44%) were sensitised to more than one allergen (polysensitised group). The mean age of the monosensitised group was significantly younger than that of the polysensitised group (58.9 ± 11.3 vs. 63.5 ± 10.9 months, *P* = 0.022). The proportion of polysensitised subjects increased gradually with age, from 8.4% (95% CI, 2–15%) at 3 years to 22.4% (95% CI, 13–31%) at 6

Table 4 Multiple logistic regression analysis of risk factors for current asthma, rhinoconjunctivitis and eczema (odds ratio (95% confidence interval))

	Current asthma	Current rhinoconjunctivitis	Current eczema
Age, months	0.98 (0.95–1.00)*	1.0 (1.0–1.0)	1.0 (1.0–1.0)
Gender (male)	0.7 (0.4–1.1)	1.2 (0.7–1.9)	1.1 (0.7–1.8)
Parental asthma	1.9 (0.9–4.2)	1.1 (0.4–2.2)	1.7 (0.7–4.4)
Pets at home	1.1 (0.3–3.6)	1.7 (0.6–5.4)	1.2 (0.4–3.7)
Secondary smoking	1.4 (0.9–2.5)	0.7 (0.4–1.1)	1.2 (0.7–1.9)
Prematurity	1.2 (0.3–4.3)	1.2 (0.4–3.7)	0.8 (0.2–2.7)
Eczema before age 2 years	2.1 (1.0–4.2)*	4.1 (2.2–7.6)**	31.2 (15.1–64.1)**
Atopic			
Monosensitisation	2.1 (1.1–4.1)*	1.7 (0.9–3.2)	2.1 (1.0–4.3)*
Polysensitisation	1.5 (0.7–3.4)	3.0 (1.4–5.0)**	2.1 (0.95–4.7)

* $P < 0.05$; ** $P < 0.005$.

years ($P = 0.002$). This increase was due to an increase in sensitisation to pollen, from 3.6% (95% CI, 2–15%) at 3 years to 21.2% (95% CI, 13–31%) at 6 years ($P < 0.001$). Children sensitised to aero-allergens only were older than children sensitised to food allergens only (62.0 ± 10.8 months vs. 44.8 ± 4.6 months, $P = 0.012$). Most monosensitised (76%, 95% CI 66–86%) and polysensitised subjects (93%, 95% CI 86–100%) were sensitive to dust mites. Among atopic children, the percentage of children sensitised to dust mites increased with age (63.6% (95% CI, 42–85%) for 3-year-olds to 92.9% (95% CI, 83–100%) for 6-year-olds ($P = 0.005$). Therefore, the positive association between sensitisation rates to dust mites and atopy increased gradually with age. Dust mite (*D. pteronyssinus*) was the most common sensitizer in all age groups.

Allergic symptoms and sensitisation

Table 4 shows the results of our multivariate logistic regression analysis of risk factors for asthma and allergic disease. Overall, the results indicate that sensitisation to allergens increased the risk for asthma and allergic diseases. Monosensitisation was a significant risk factor for current asthma (OR = 2.1 (95% CI, 1.1–4.1), $P = 0.024$) and current eczema (OR 2.1 (95% CI, 1.0–4.3), $P = 0.042$). Polysensitisation (OR = 3.0 (95% CI, 1.4–5.0), $P = 0.005$) and eczema in the first 2 years of life (OR = 4.1 (95% CI, 2.2–7.6), $P = 0.033$) were significant risk factors for current rhinoconjunctivitis. Gender, pet ownership, exposure to tobacco smoke, prematurity or low birthweight and parental asthma were not significant independent risk factors for allergic diseases.

Discussion

Our results indicate that the patterns of sensitisation to allergens and allergic symptoms depend on the age of pre-school children. Dust mite was the major allergen, and the agreement between sensitisation to dust mite and atopy increased gradually with age. Although the presence of eczema in the first 2 years of life increased the risk for current rhinoconjunctivitis (a step in the allergic march), age-related changes in the pattern of sensitisa-

tion to allergens (such as polysensitisation) were independently related to current rhinoconjunctivitis. Therefore, careful follow-up of changes in sensitisation patterns may provide a better understanding of the pathogenesis of the allergic march.

Our results indicate that the prevalence rates of current asthma, rhinoconjunctivitis and eczema in 6-year-olds were 8.2%, 21.2% and 15.3%, respectively. Comparison of our results with the phase III ISAAC study of 6- to 7-year-olds indicated that: (i) our prevalence of asthma symptoms was lower than in Germany (12.8%) and New Zealand (22.2%); (ii) our prevalence of rhinoconjunctivitis symptoms was higher than in Germany (6.9%), the UK (10.1%) and New Zealand (11.4%); and (iii) our prevalence of eczema symptoms was similar to that of Germany (7.9%), the UK (16.0%) and New Zealand (15.0%).⁴

Our results indicate that the prevalence of current asthma decreased markedly with age. This could be because we could not completely exclude subjects who experienced transient wheezing. Wheezing in pre-school children is a heterogeneous symptom, and multiple pathological processes may be involved. Therefore, it is difficult to distinguish young children with asthma from those with transient symptoms only. Thus, there were no significant differences in the prevalence of 'asthma diagnosis by a physician' among age groups (data not shown). Interestingly, the prevalence of current rhinitis increased dramatically with age. Although not all children with current rhinitis necessarily had allergic rhinitis, this result is consistent with previous studies that demonstrated that the prevalence of rhinitis markedly increased with child age.^{12,21} There was no difference in the prevalence of current eczema among age groups, possibly due to the increased prevalence of newly diagnosed eczema after 2 years of age. However, in this study, parents filled in the ISAAC questionnaire. Therefore, recall bias and reporting bias cannot be excluded.

The prevalence of atopy is 1.7–45.3% worldwide.²² The sensitisation to allergens at age 6 years in our study (33%) is comparable to that reported in German studies,⁹ but much higher than that observed in previous studies.^{16,23,24} Although atopy did not differ according to age, age can impact the number (mono- vs. polysensitisation) and type (food or inhalant

allergens) of allergen sensitisation,^{25,26} a finding consistent with previous investigations.^{22,24} This change in mono- and polysensitisation was notable in the transitional period of four age groups, as was the change in food and aero-allergen sensitisation. This age range was similar to a previous study.²⁷ Our findings suggest that sensitisation to allergens in pre-school children is a dynamic process and that the process of sensitisation occurs between ages 2 and 4 years.

The pattern of sensitisation to specific allergens appears to depend on geographic region.^{2,4} As expected, the most common allergen identified in both mono- and polysensitised children was house dust mite. The rate of sensitisation to house dust mite in our 4-year-old age group (17%) was greater than that reported in Western studies (12% at 4 years old²⁵ and 4% at 5 years old).⁹ This is probably due to the high levels of humidity in Korea,²⁸ which provide an ideal habitat for dust mite growth.²⁹

Quite strikingly, most atopic Korean pre-school children were sensitised to dust mite, and the agreement between sensitisation to dust mite and atopy increased with age. It could be that sensitisation to house dust mite is the start of sensitisation to aero-allergens and polysensitisation. Such a process probably impacts the agreement between sensitisation to dust mite and atopy in pre-school children. Therefore, sensitisation to dust mite at an early age may be a predictor for the development of aero- and polysensitisation in children aged 6 years and older. These results also suggest that, depending on the geographic region, the pattern of allergen sensitisation can affect allergic disease.^{9,10,30}

Importantly, we demonstrated that polysensitisation was a significant independent risk factor for current rhinoconjunctivitis. A previous study reported that polysensitised children were more likely to have polysensitised parents and severe clinical atopic phenotypes than monosensitised children.^{25,31,32} Polysensitisation had a graded effect, with the potent factors, such as familial atopy and dust mite, having the greatest impact. Therefore, it appears that the allergic march is more significantly associated with polysensitisation than monosensitisation.

In conclusion, our study of pre-school children indicated that by the age of 4 years, allergic symptoms and sensitisation patterns change significantly and that these factors significantly impact each other. Primary sensitisation to dust mite may be a predictor of atopy and subsequent polysensitisation; thus, it seems to play an important role in the development of allergic diseases. We suggest further study of the changes in allergen sensitisation patterns in pre-school children in order to better understand the allergic march.

Acknowledgement

The Korean version of ISAAC was provided by the Korean Pediatric Allergy and Respiratory Society.

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