

REGULAR ARTICLE

Can sensitization to aeroallergens disappear over time in children with allergic disease?

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Abstract

Background: Remittance of aeroallergen sensitization has been shown in population-based studies, but there is a common perception that sensitization to aeroallergens rarely if ever disappears in children with allergic disease.

Methods: We retrospectively reviewed all specific IgE tests carried out in children aged 0–18 years at our hospital laboratory over a 14-year period. Of 3115 children sensitized to one or more aeroallergens, 244 (7.8%) were retested after a mean (SD) period of 45 (28) months at their physician's discretion.

Results: Disappearance of sensitization to individual aeroallergens did occur, with remittance rates ranging from 3.1% for house dust mite to 17.5% for cat. However, complete remittance of aeroallergen sensitization was found in only one subject. In up to 35% of cases, remittance of sensitization was offset by the appearance of one or more new aeroallergen sensitizations. Remittance was only observed in children sensitized to multiple allergens (with a median of 3 aeroallergen sensitizations), and their median degree of sensitization was low (median 2.1 kU/L).

Conclusion: Aeroallergen sensitization can disappear in children with allergic disease, but only in polysensitized individuals. Complete remittance of sensitization to aeroallergens is rare in symptomatic children.

INTRODUCTION

Population studies show that sensitization to allergens follows a specific pattern in childhood. During the first years of life, sensitization to food allergens predominates, and sensitization to aeroallergens is rare (1–3). Between the ages of 1 and 6, sensitization rates to food allergens decrease, while aeroallergen sensitization increases (1–3). The increase in aeroallergen sensitization then continues throughout the schoolage period and adolescence (4–8).

This 'atopic march' of increasing aeroallergen sensitization rates during the first 20 years of life has fuelled the common perception that aeroallergen sensitization, once established, rarely if ever disappears in childhood. Three population-based studies have shown, however, that such remittance, although rare, is possible. A birth cohort study from Arizona found that sensitization to seasonal pollen disappeared in 8.2% of children between the ages of 6 and 11 years (9). In earlier studies from Western Europe with a follow-up of 2 years, remittance rates of sensitization to aeroallergens ranging from 5% to 12.1% were found (6,7). We set out to investigate whether disappearance of sensitization to aeroallergens can also occur in children presenting to a doctor with symptoms of allergic disease.

METHODS

This was a retrospective analysis of all specific IgE tests carried out in children aged 0–18 years at our hospital's Clinical Laboratory between 1 January 1990 and 31 December 2003, visiting their practitioner for symptoms of allergic disease (3). The clinical laboratory of the Isala Klinieken, a large (900 beds) district general teaching hospital in Zwolle, the Netherlands, is the only laboratory in the catchment area of the hospital which performed specific IgE testing for general practitioners (GPs) and hospital-based specialists (including paediatricians, dermatologists, allergists and ear-nose-throat specialists) throughout the study period. In the Netherlands, sick children primarily visit the GP, and can only be seen by a specialist after referral by the GP.

The ImmunoCap system (Phadia Diagnostics, Nieuwegein, The Netherlands) was used for specific IgE determination throughout the study period. As the detection limit of the assay was 0.35 kU/L, sensitization to a specific allergen was defined as a specific IgE concentration of ≥ 0.35 kU/L. The most common requested test was a screening test for the major aeroallergens for children in the Netherlands (house dust mite, grass and tree pollen, dog and cat dander), which was subsequently specified if positive. The degree of sensitization was expressed as specific IgE levels in kU/L.

Specific screening for one or more aeroallergens was also available at request of the attending physician.

Population

For this analysis on changes in aeroallergen sensitization over time, only children were included which met all of the following inclusion criteria: (i) sensitization to one or more aeroallergens during any of the tests performed, (ii) re-tested for the same aeroallergen(s) at least 6 months later and (iii) age 18 years or younger at the last test. If the follow up tests were repeated more than once, only the last result was included. Children with cystic fibrosis were excluded. Remittance of sensitization was defined as a positive specific IgE tests at the first test (≥ 0.35 kU/L), followed by a negative specific IgE test for the same allergen at the second test.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL, USA), version 15.0 for Windows. Differences between proportions were analysed by chi-square test, differences between means with Student's *t*-test, and differences between medians (for non-normally distributed variables) with Mann-Whitney *U*-test.

RESULTS

Over the 19-year period, specific IgE was assessed in a total of 9044 children, 3115 of which (34%) were sensitized to one or more aeroallergens. Most of these children were tested only once; a total of 244 children (7.8% of those initially tested positive for aeroallergens) fulfilled the inclusion criteria of our study. Retesting was performed at the treating physician's discretion; the specific reasons for this were not systematically recorded in this retrospective survey. The mean (SD) age of these children at the first test was 5.7 (4.1) years (median 5 years, range 0–7 years). The mean (SD) time between the two tests was 45 (28) months. There were 123 boys (50.4%). Forty-three children (17.6%) were only tested for one or two specific allergens; complete data on specific IgE to all five aeroallergen on both occasions were available in the remaining 201 patients.

Table 1 shows the sensitization and remittance rates to each of the five aeroallergens separately. Sensitization to house dust mite was most common (68% of children tested had a positive specific IgE to this allergen), followed by

grass pollen, pets and tree pollen. Remittance of sensitization to individual allergens ranged from 3.1% for house dust mite to 17.5% for cat (Table 1). Remittance of outdoor allergens (grass or tree pollen) was less common (5.6%) than for indoor allergens (house dust mite, cat and dog; 8.9%), but the difference was not significant ($p = 0.22$).

Table 2 shows the changes in the number of specific sensitizations over time in the 201 children who had complete data on all aeroallergens at both occasions. The median number of sensitizations increased from the first test [median 2, interquartile range (IQR): 1–3] to the second (median 3, IQR: 2–4, $p = 0.001$), although it decreased in 19 children (9.5%).

Overall, remittance of any given sensitization occurred in 28 (13.5%) of the children. Remittance of one sensitization occurred in 19 of those 28 (68%), and of two or more sensitizations in the remaining 9 (32%). However, complete remittance of sensitization to all aeroallergens was found in only one subject. In many cases, remittance of a specific sensitization was offset by the appearance of a specific sensitization to another aeroallergen. This is illustrated for the 20 subjects initially sensitized to cat in Table 3. Remittance of cat sensitization was offset by appearance of one or more new sensitizations in seven subjects (35%). This 'offset rate' was 0–20% for the other allergens.

Characteristics of the 28 subjects who showed disappearance of sensitization to one or more aeroallergens are shown in Table 4. These 28 subjects were all initially sensitized to two or more aeroallergens (house dust mite in 20, grass pollen in 16, tree pollen in 13, cat in 23 and dog in 17 subjects respectively); such polysensitization was present in 107/173 children (61.8%) in whom no remittance of aeroallergen sensitization was found ($p < 0.001$). Additional food allergen sensitization was found in each of the 11 subjects in whom this was also tested.

Further analyses were carried out to examine predictive factors for remittance for any allergen sensitization. Remittance was not associated with gender [14/28 subjects (50%) who showed remittance were boys, when compared with 89/173 (51.4%) of those without remittance, $p = 0.89$]. Similarly, neither age at initial testing [mean (SEM) age 6.7 (0.85) and 5.5 (0.31) years, respectively, $p = 0.19$] nor the time period between the two test occasions [3.3 (SEM 0.17) years and 4.0 (0.4) years, respectively, $p = 0.53$] differed between the two groups. The number of sensitizations at the initial test was higher (median 3, IQR: 2–4) in children in whom remittance of any sensitization was found than in

Table 1 Sensitization and remittance rates of each of the five specific aeroallergens

	House dust mite	Cat	Dog	Grass pollen	Tree pollen
Number tested at both occasions	238	234	232	219	207
Positive first test, n (%)	162 (68.1)	114 (48.7)	104 (44.8)	121 (55.3)	59 (28.5)
Remittance*, n (%)	5 (3.1)	20 (17.5)	9 (8.7)	5 (4.1)	5 (8.5)

*Remittance of sensitization was defined as a positive specific IgE tests at the first test, followed by a negative specific IgE test for the same allergen at the second test.

Table 2 changes in the number of specific aeroallergen sensitizations to the five most common aeroallergens from the first to the second test

Number of positive sensitizations at first test	Number of positive sensitizations at second test					
	0	1	2	3	4	5
1 (66)	0	33	16	5	6	6
2 (54)	0	2	20	15	8	9
3 (34)	0	3	5	7	14	5
4 (27)	1	1	1	3	14	7
5 (20)	0	0	0	3	0	17

Table 3 changes in sensitization patterns in the 20 children initially sensitized to cat who showed remittance of cat allergen sensitization at the second test

Subject	Sensitizations at first test	Sensitizations at second test
1	HDM, grass, tree, cat, dog	HDM, grass, dog
2	HDM, grass, cat, dog	HDM, grass, dog
3	Grass, tree, cat, dog	Grass, tree, dog
4	Grass, tree, cat, dog	Grass, tree
5	HDM, tree, cat, dog	HDM
6	HDM, grass, cat, dog	None
7	Grass, cat, dog	HDM, grass, dog
8	HDM, tree, cat	HDM, tree
9	HDM, grass, cat	HDM, grass
10	HDM, cat, dog	HDM, dog*
11	HDM, grass, cat	Grass
12	Tree, cat, dog	Tree
13	Cat, dog	HDM, grass, tree, dog
14	Cat, dog	HDM, grass, dog
15	HDM, cat	HDM, grass, dog
16	HDM, cat	HDM, dog**
17	HDM, cat	HDM, grass
18	Grass, cat	Grass, tree
19	HDM, cat	HDM
20	HDM, cat	HDM

HDM = house dust mite.

*Patient was only tested for indoor allergens (HDM, cat, and dog) at first test.

**Patient was only tested for HDM, cat, dog and grass pollen (not for tree pollen) at second test.

Table 4 clinical characteristics of 28 subjects in whom sensitization to one or more aeroallergens disappeared over time

Male sex, n (%)	14 (50)
Diagnosis, n (%)	
No clinical information available	14 (50)
Asthma	5 (18)
Atopic dermatitis	4 (14)
Allergic rhinitis	2 (7)
Other (gastrointestinal symptoms, urticaria, anaphylaxis)	3 (11)
Mean (SD) age, years	6.7 (4.5)
Median (IQR) total serum IgE, kU/L	233 (14–1704)
Initially sensitized to, n (%)	
0 or 1 aeroallergen	0 (0)
2 aeroallergens	8 (28.6)
3 aeroallergens	10 (35.7)
4 aeroallergens	7 (25)
5 aeroallergens	3 (10.7)

those without any remittance (median 2, IQR: 1–3, $p < 0.001$). Similarly, the degree of sensitization was higher in those who remitted than in those who did not, for

example, for cat allergen: median 2.1, IQR: 0.7–3.5 kU/L and median 0, IQR: 0–3.5 kU/L respectively ($p = 0.002$). We refrained from examining the importance of these factors in multiple logistic regression models because of the low prevalence of remittance, and because of the interdependence of these factors.

DISCUSSION

This study shows that sensitization to aeroallergens is not always a permanent phenomenon, and that it can remit even in children visiting a doctor with symptoms of allergic disease. Remittance rates varied between allergens from 3.1% for house dust mite to 17.5% for cat (Table 1). Complete remittance of sensitization to all aeroallergen, however, was very rare: almost all children remained sensitized to other aeroallergens, and in a significant minority, remittance of one specific aeroallergen sensitization was offset by the appearance of another. Disappearance of sensitization to one or more aeroallergens almost exclusively occurred in children sensitized to multiple aeroallergens. The median degree of aeroallergen sensitization in these ‘remitters’ was low (2.1 kU/L).

Few studies to date have examined dynamic changes in aeroallergen sensitization over time. Early studies in Arizona (USA) and Australia reported very low remittance rates (4,5). In the Arizona prospective cohort study, no children younger than 14 years of age showed complete remittance of aeroallergen sensitization over a period of 8 years; no data were given on remittance rates of sensitization to individual aeroallergens (5). In the Australian study, remittance of aeroallergen sensitization was only seen in 1% of 8- to 10-year-old children over a period of 2 years (4). In this study, a higher cut-off value for sensitization (skin prick test wheal size ≥ 4 mm) was used than in most studies (2,6–10). As remittance was more common for aeroallergens with a low degree of sensitization, it is possible that these were not included in the Australian study.

Later population-based studies in the UK, Arizona and Austria did show remittance of specific aeroallergen sensitization (6,7,9), which appears to be in accordance with our results. In a population-based sample of children with mild respiratory symptoms, Johnston et al. showed remittance of aeroallergen sensitization in 7% of children when retested after 2 years (7). In a birth cohort from Arizona, 8.2% of children who were sensitized to one or more local pollen allergens at the age of 6 years were no longer sensitized to aeroallergens at 11 years of age (9). In a large cohort of schoolchildren from Austria and Germany, remittance of individual aeroallergen sensitization varied from 5% to 12.1% after 3 years (6). These remittance rates are comparable with those in our study after a mean follow-up of almost 4 years (Table 1). The largest study examining the dynamic process of aeroallergen sensitization in children was recently reported from Sweden. In this cohort of more than 2000 children followed up prospectively to the age of 8 years, remittance of aeroallergen

sensitization between the ages of 4 and 8 years ranged from 3% to as much as 31% for different allergens (11). Remittance was more likely in children sensitized to multiple allergens, and for allergens with a relatively low degree of sensitization; this is in accordance with our results.

All the previous studies were population-based studies which has the advantage of offering insight into the dynamics of aeroallergen sensitization at a general population level. These results, however, are not directly applicable in the clinical situation, where tests of allergic sensitization are performed in children visiting a doctor with symptoms of allergic disease. To our knowledge, our study is the first to examine changes in aeroallergen sensitization over time in children with symptoms of allergic disease. Our data, therefore, are complementary to the results from population-based studies. In addition to its clinical setting, the main strength of our study is the large sample size. The main disadvantage is the lack of clinical information on the patients in our study. As a result of the relatively low prevalence of remittance, it was impossible to explore the independent influence of various factors on remittance in multiple regression models.

Remittance of individual aeroallergen sensitization was most commonly found in children sensitized to multiple allergens. Despite being very common (12–14), this phenomenon of polysensitization in childhood is poorly understood. We and others have recently shown a relationship between total serum IgE level and the risk of polysensitization (14,15). In such polysensitized children, specific IgE levels to any given allergen should be interpreted with caution (14). As our present study shows, sensitization to any given allergen may not persist over time (Tables 2 and 3). This was most common for cat allergen sensitization in our study (Table 1). It has also been shown that sensitization patterns in polysensitized individuals cannot be explained by cross-reactivity to biologically similar allergens (14). It appears, therefore, that polysensitization in childhood is a distinct clinical phenotype of allergic disease. Adults with polysensitization appear to have more severe symptoms and a worse quality of life than monosensitized patients (16). Whether this also applies for children remains to be established.

In conclusion, this study shows that aeroallergen sensitization may disappear in children visiting a doctor with symptoms of allergic disease, but only in children with polysensitization. Complete remittance of aeroallergen sensitization is very rare in symptomatic children.

CONFLICT OF INTEREST

None declared.

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