

Atopy in wheezing infants always starts with monosensitization

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ABSTRACT

Previously, evidence has been provided that sensitization is frequent in asthmatic children and polysensitization represents the natural history of allergy. The aim of this study was to investigate whether polysensitization may occur primarily in infants with wheezing. Thus, 98 infants (<1 year of age) were studied at the onset of wheezing symptoms. All children underwent three visits (each including skin-prick test): at baseline and after 2 and 5 years. At onset of wheezing, ~20% of infants were sensitized, whereas at 6 years the percentage was >60%. The most important finding was that there was no polysensitized infant at baseline, whereas most of the sensitized children were polysensitized at 6 years. Moreover, the number of sensitizations increased with age. House-dust mites were the most important cause of allergic symptoms. Wheezing may disappear mainly in nonallergic children. In conclusion, this study provided the first evidence that respiratory allergy always starts with monosensitization and confirms previous studies concerning the natural history of allergy characterized by the progression toward polysensitization.

(Allergy Asthma Proc 28:449–453, 2007; doi: 10.2500/aap.2007.28.2966)

Key words: Allergen, asthma, longitudinal, monosensitization, natural history, polysensitization, prevalence, prospective, skin test, wheezing

The sensitization to an allergen plays a major role as a risk factor for the development of asthma.^{1,2} Particularly, sensitization to indoor allergens (including house-dust mites and pets) and certain outdoor allergens (including pollens and mold spores) has been found to increase the risk of asthma symptoms and bronchial hyperresponsiveness in children.³

In general, approximately two-thirds of asthmatic patients are sensitized to at least one inhalant allergen.⁴ In addition, this percentage is higher in adolescents and young adults as reported previously.^{5,6}

The phenomenon of sensitization is linked directly to the altered immune response to allergens in atopic subjects, because recent evidence indicates that allergic subjects have a defect in T-regulatory cells.⁷ Note that this defect may be filled by specific immunotherapy.⁸ Recently, we provided evidence that lymphocytes of untreated allergic patients do not produce IL-10, whereas allergic subjects successfully treated with sublingual immunotherapy show an *in vitro* synthesis of

IL-10.⁹ In this regard, it has been proposed that allergic diseases should be considered as immunoregulatory disorders.¹⁰

It is well known that the sensitization process progressively develops from childhood to adulthood. We previously indicated that polysensitization frequently occurs in asthmatic children because some of them were already polysensitized at 3 years.¹¹ Thus, in this study we aimed at verifying whether polysensitization still may be present at the onset of wheezing symptoms in infants.

MATERIALS AND METHODS

Study Design

This study aimed at evaluating longitudinally and prospectively the characteristics of sensitization and wheezing symptoms in a large group of infants. The infants (<1 year of age) initially were visited at the onset of respiratory symptoms. Careful history, physical examination, and skin-prick test (SPT) were performed during the visit. All children were followed for the successive 5 years and underwent SPT for the same panel of allergens 2 and 5 years after the first visit. Outcomes of this study described the course of the percentage of allergic and nonallergic children over time and to evaluate the course of sensitization in allergic children over time. Parental consent was obtained for all children.

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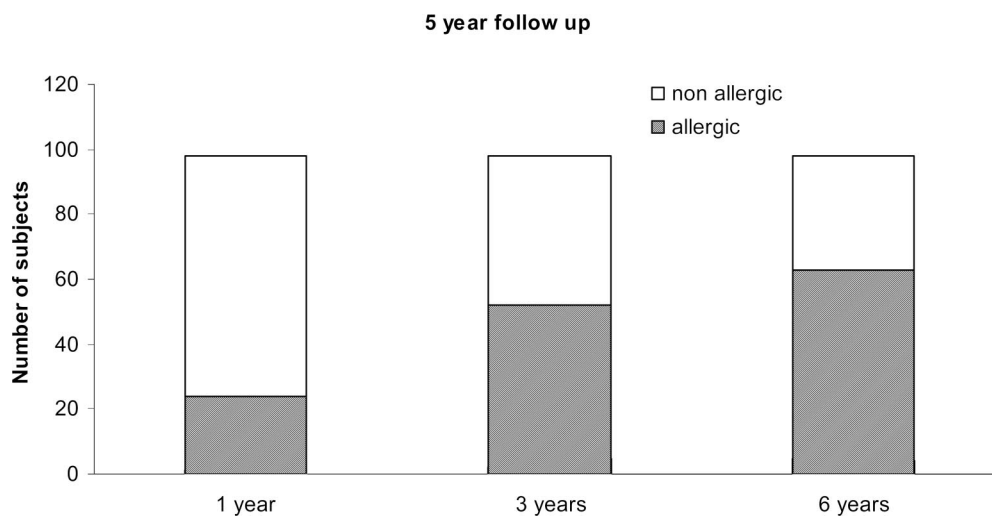


Figure 1. Distribution of sensitized children at different ages.

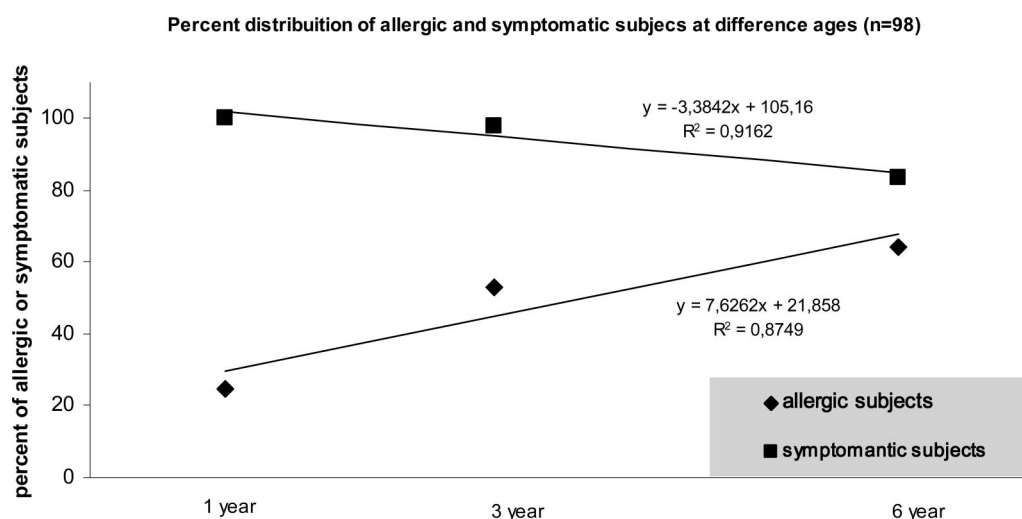


Figure 2. Distribution of the percentage of sensitized subjects at different ages. Line represents linear regression.

Subjects

The enrolled infants (98 with 68 male and 30 female infants) were followed up for 5 years. Wheezing was diagnosed clinically according to Global Initiative for Asthma criteria.¹² No child suffered from anatomic alterations of the upper airways, immunologic deficiencies, or major systemic diseases (diabetes, anemia, cystic fibrosis, and/or inherited metabolic disorders). No child had a history of cardiac disease and/or arrhythmia.

SPT

Allergy was assessed by the presence of sensitization to the most common classes of aeroallergens by performing an SPT. It was performed, as stated by the European Academy of Allergy and Clinical Immunology.¹³ The allergen panel consisted of the fol-

lowing: house-dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cats, dogs, grasses mix, *Compositae* mix, *Parietaria officinalis*, birch, olive trees, and *Alternaria tenuis*; the concentration of allergen extracts was 100 IR/mL (Stallergenes, Milan, Italy). The tested allergens were chosen based on our previous studies in which they represented the prevailing sensitization in Ligurian children.^{6,11}

A histamine solution in distilled water (10 mg/mL) was used as positive control and the glycerol-buffer diluent of the allergen preparations was used as negative control. Each patient was skin tested on the volar surface of the forearm using 1-mm prick lancets (Stallergenes). The skin reaction was recorded after 15 minutes by evaluating the skin response rate to the inoculation of each allergen extract in comparison with the wheal given by

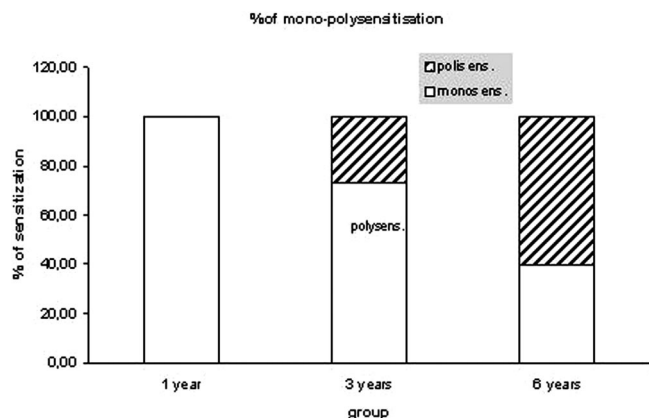


Figure 3. Percentages of mono- and polysensitized children during the 5-year follow-up.

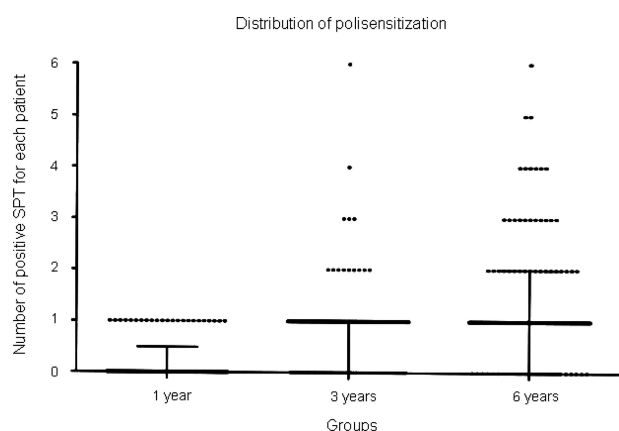


Figure 4. Number of sensitizations during the 5-year follow-up.

the positive and the negative control. A wheal diameter ≥ 3 mm was considered a positive reaction. Antihistamines were stopped 1 week before SPT.

Sensitization Score

For each allergic child a score was calculated by adding the number of positive allergens at SPT. The score started at 1 (monosensitization).

Statistical Analysis

SPT results were analyzed by the nonparametric McNemar test to value significantly differences in single allergen sensitization from the first to the latest visit. The decreasing of respiratory symptoms from the first to the latest visit were analyzed by the nonparametric McNemar test. Sensitization score variations in different age groups were tested with the nonparametric Mann-Whitney *U* test. The score sensitization values are expressed as the median plus/minus upper and lower quartiles. The variations of agreement between respiratory symptoms and positivity/negativity to the SPT were analyzed by χ^2 -test.

Values of $p < 0.05$ were considered statistically significant.

RESULTS

The percentage of change of allergic and nonallergic children during the 5-year follow-up is described in Fig. 1. At baseline, 24 infants were allergic (24.49%). After 2 years, 52 children were allergic (53.06%), and after 5 years 63 children were allergic (64.29%). The percent distribution of allergic subjects and symptomatic subjects at different ages is shown in Fig. 2. At

Allergic childrens. Six years follow up.

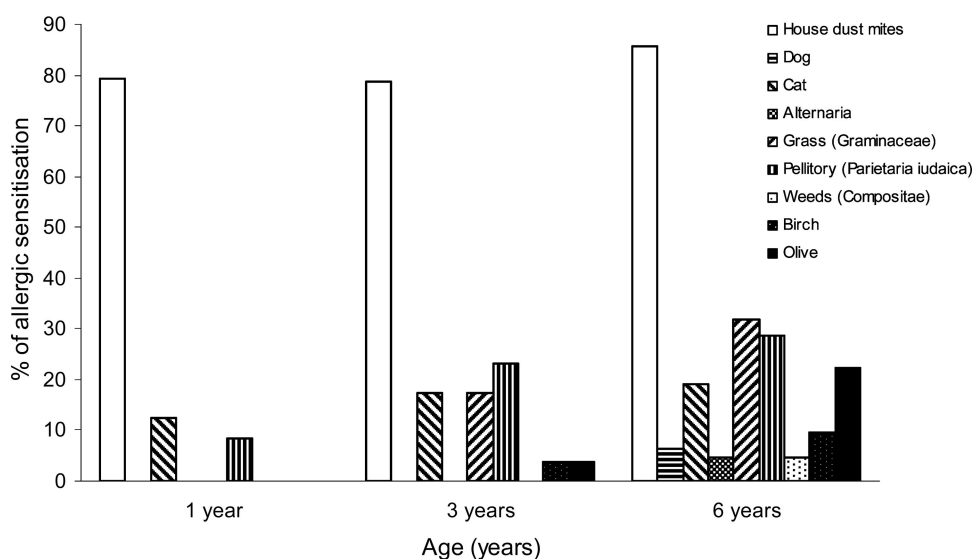


Figure 5. Percentage of sensitization to a single allergen. Data were calculated as percent between the number of single sensitizations and the number of allergic children.

Table 1 Analysis of significant changes for single allergens (McNemar test) during the 5-yr follow-up

SPT	1 yr vs. 3 yr	3 yr vs. 5 yr
House-dust mites	<0.0001	0.0009
Dogs	NS	NS
Cats	0.0412	NS
<i>Alternaria</i>	NS	NS
Grasses	0.0077	0.0026
<i>Parietaria</i>	0.0044	0.0412
<i>Compositae</i>	NS	NS
Birch	NS	NS
Olive trees	NS	0.0015

NS = not significant.

Table 2 Distribution of monosensitization during the 5-yr follow-up

SPT	1 yr	3 yr	5 yr
House-dust mites	79.17	78.95	92.00
Dogs	0.00	0.00	0.00
Cats	12.50	5.26	4.00
<i>Alternaria</i>	0.00	0.00	0.00
Grasses	0.00	5.26	4.00
<i>Parietaria</i>	8.33	10.53	0.00
<i>Compositae</i>	0.00	0.00	0.00
Birch	0.00	0.00	0.00
Olive trees	0.00	0.00	0.00

baseline, all subjects were symptomatic, whereas after 2 years 3 children were without symptoms and after 5 years 16 children were without symptoms.

Figure 3 shows the percentage of mono- and polysensitized children during the 5-year follow-up. At baseline, no infant was polysensitized, whereas after 2 years 24% of allergic children were polysensitized, and after 5 years 57% of allergic children were polysensitized. The distribution of the number of sensitizations during the 5-year follow-up is shown in Fig. 4; the number of sensitizations clearly increases with age. Figure 5 shows the percentage of positivity to the single allergens; house-dust mites were the most relevant allergen.

Table 1 shows the analysis of significant changes by McNemar test concerning the single allergens; house-

Table 4 Analysis of the decreasing of wheezing (McNemar test)

	1 yr vs. 3 yr	3 yr vs. 6 yr
Reduction of wheezing	0.48	0.002

Table 5 Analysis of variation of agreement between respiratory symptoms and positivity/negativity to SPT (χ^2 -test)

$p < 0.001$	Agreement	Disagreement
1 yr	24	74
3 yr	53	45
6 yr	73	25

Table 6 Number of nonsymptomatic children at different ages

Nonsymptomatic	1 yr	3 yr	6 yr
Total number	0	2	16
Monosensitizations	/	1	2
Polysensitizations	/	/	1

dust mites significantly increased over time as well as cat allergen, grasses, *Parietaria*, and olive trees. Table 2 shows the distribution of monosensitization for each single allergen during the study; house-dust mites are the most important cause of monosensitization over time, whereas all the other allergens were rarely or never a cause of monosensitization.

Table 3 analyzes the changes in the sensitization score; there is a constant trend to increase the number of sensitizations over time. Table 4 shows the trend of reduction of wheezing symptoms over time; there is a significant change between 3 and 6 years of age. Table 5 analyzes the variation of agreement between respiratory symptoms and atopy; only at 6 years of age was there an association between sensitization and wheezing. Table 6 shows the number of children without symptoms at 3 and 6 years of age related to mono- or polysensitization; there is no association.

Table 3 Analysis of changes in the sensitization score (Mann-Whitney test)

	Age Group			Mann-Whitney U Test p Value	Polysensitization Trend
	1 yr	3 yr	6 yr		
Median	0.0	1.0	1.0	1 yr vs. 3 yr, <0.0001	Rise up
Lower quartile	0.0	0.0	0.0	3 yr vs. 6 yr, 0.0042	Rise up
Upper quartile	0.5	1.0	2.0	1 yr vs. 6 yr, <0.0001	Rise up

DISCUSSION

Wheezing in early childhood may persist, becoming asthma, or may remit. Frequently, persistent wheezing is associated with atopy.¹⁴ Actually, even though asthma is a polyfactorial syndrome, IgE-mediated reaction is involved frequently in asthma immunopathology.^{15,16}

Previously, we have provided evidence that (i) sensitization is very frequent in asthmatic children, (ii) polysensitization represents the natural history of allergy, and (iii) the type of immune response appears different for each single allergen.¹¹ Moreover, in that study we reported that polysensitization may be already present at 3 years; thus, we aimed at investigating whether this phenomenon may occur at the early onset of wheezing symptoms. Therefore, we designed this study to assess infants at the onset of wheezing to follow-up them for 5 years.

The findings suggest several considerations. First, sensitization represents a phenomenon that typically increases with age because only 20% of infants were sensitized, whereas >60% children who were 6 years old were allergic. Second, wheezing may disappear in older children and the trend is inversely related to sensitization. It should be noted that most of the children with remittent wheezing are nonallergic. In other words, atopy represents a risk factor for asthma development. This finding confirms previous evidence.¹¹ Third, no infant was polysensitized at the early onset of wheezing symptoms. This finding is the most important result of the study because it provides the first evidence that allergy always starts as monosensitization. In fact, because we previously evidenced that polysensitization constitutes the natural history of allergic subjects, this survey clearly indicates that every atopic patient is monosensitized at the onset of clinical events. This issue establishes a fundamental clinical relevance: specific treatment oriented to prevent the natural progression of allergic disorders has to be prescribed early. In this regard, specific immunotherapy has been shown to prevent polysensitization occurrence.^{17,18}

Fourth, the number of sensitizations increase in a parallel manner with age. Furthermore, this fact confirms the concept of the progression of polysensitization as previously reported.¹¹ Fifth, this study confirms that house-dust mites are the most important causal allergen involved in wheezing children as previously broadly established.^{5,6,11}

In conclusion, this study answers the primary question asked by the previous study¹¹: polysensitization is a secondary phenomenon that always follows monosensitization.

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