

The natural history of allergy: the development of new sensitizations in asthmatic children

Lilia Fasce^a, Maria Angela Tosca^a, Roberta Olcese^a, Manlio Milanese^b,
Daniela Erba^a, Giorgio Ciprandi^{c,*}

^a *I Clinica Pediatrica and Istituto Giannina Gaslini, Genova, Italy*

^b *Respiratory Physiopathology, University of Genoa, Genova, Italy*

^c *Allergologia-U.O. ORL, Dipartimento Regionale Testa-Collo, Padiglione Specialità (piano terzo),
Ospedale San Martino, Largo R. Benzi 10, 16132 Genova, Italy*

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Abstract

Allergy is an important risk factor for asthma in children as most of asthmatic children are sensitized.

The aim of the study was to investigate the natural course of sensitizations in a group of children (340) at the onset of asthmatic symptoms. We subdivided children in three groups depending on the age at first visit (3–7–11 years) and followed them for 4 years. All children underwent three visits, each including skin prick test, every two years.

In the 3-year age group ($n = 133$), 59% of children were sensitized at first visit, but the percentage increase to 88% at third visit.

When looking only at allergic children at first visit (261), we demonstrated that polysensitization became higher than monosensitization since the age of 11. Analysis of sensitization distribution over the time revealed that house dust mites were prominent from the age of 3 years. *Parietaria* and grass pollens as well as olive pollen significantly increased, particularly during the 4-year follow-up in the 7-year group.

Analysis of sensitization score demonstrated that the age range from 3 to 11 is at high risk to polysensitization.

In conclusion, this study provides evidence that sensitization is frequent in asthmatic children, polysensitization represents the natural history of allergy and the type of immune response should appear different for each allergen.

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1. Introduction

Allergen sensitization plays a major role as risk factor for the development of asthma [1,2]. Sensitization to indoor allergens 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].

Approximately two thirds of asthmatic patients are sensitized to at least one inhalant allergen [4]. Moreover, this percentage is higher in adolescents and young adults as reported also by ourselves [5,6].

The phenomenon of sensitization is directly linked to the altered immune response to allergens in atopic sub-

jects. Atopy is characterized by a predisposition to specific IgE production. This predisposition is genetically determined. Allergic subjects show a typical T helper 2 (Th2)-polarization and Th2-derived cytokines (including IL-4, IL-9, and IL-13) play a critical role in promoting, maintaining, and amplifying IgE synthesis [7].

It is well known that the sensitization process progressively develops from childhood to adulthood, even though we do not know how this phenomenon changes as time goes on and how different sensitizations act on subjects. The degree and type of sensitization may be related to genetic factors but also to the concentration and the duration of allergen exposure.

Few studies investigated the time-course of sensitization process in asthmatic children and most of them were cross-sectional [8,9]. Thus, the present study aimed at evaluating prospectively the characteristics of sensitization in a group of asthmatic children.

* Corresponding author. Tel.: +39-010-5552124;
fax: +39-010-5556682.

E-mail address: gio.cip@libero.it (G. Ciprandi).

2. Materials and methods

2.1. Study design

This study aimed at evaluating longitudinally and prospectively the characteristics of sensitizations in a large group of asthmatic children.

The children were initially visited at the onset of respiratory symptoms, including wheezing, dyspnoea, cough, and breath shortness. Careful history, physical examination, and skin prick test were performed during the visit.

All children were followed for the successive 4 years and underwent skin prick test for the same panel of allergens every 2 years.

Objectives of the study were to describe the course of allergic and non allergic 3 years old children percentage over the time, and to study the course of sensitizations in allergic children at different age groups over the time.

Parental consent was obtained for all children.

2.2. Subjects

The enrolled children (222 males and 118 females) were subdivided into three groups according their age at first visit and followed up for 4 years. Therefore, they were 3, 7, and 11 years old. This sub-division was made according with the common International sub-division of pediatric ages (preschool years, early school years, adolescence) [10].

Asthma was clinically diagnosed according to GINA criteria [11]. No child suffered from anatomical alterations of the upper airways, immunologic deficiencies or major systemic diseases (diabetes, anaemia, cystic fibrosis, inherited metabolic disorders). No child had a history of cardiac disease and/or arrhythmia.

2.3. Skin prick test (SPT)

Allergy was assessed by the presence of sensitization to the most common classes of aeroallergens by performing skin prick test. It was performed, as stated by the Italian Society of Allergy and Clinical Immunology [12]. The allergen panel consisted of the following: house dust mites (*Dermatophagoides farinae* and *pteronyssinus*), cat, dog, grasses mix, *Compositae* mix, *Parietaria officinalis*, birch, olive tree, *Alternaria tenuis*; the concentration of allergen extracts was 100 I.R./ml (Stallergenes, Milan, Italy).

The tested allergens were chosen on the basis of our previous study in which they represented the prevailing sensitization in Ligurian children [6,9].

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

with the wheal given by the positive and the negative control. A wheal diameter equal or greater than 3 mm was considered a positive reaction. Antihistamines were stopped 1 week before skin prick test.

2.4. Sensitization score

For each allergic children a score was done by adding the number of positive allergen at SPT. The score started from 1 (monosensitization).

2.5. Statistical analysis

SPT results during the follow-up period was analyzed by McNemar test comparing nominal data at first and last visit. Sensitization score during the follow-up period was analyzed by Kruskal–Wallis test and when significance was obtained by *U* Mann–Whitney comparing non parametric data between two groups. $P < 0.05$ was considered statistically significant. Data are expressed as median (upper–lower quartiles).

3. Results

3.1. Three years old group

Fig. 1 describes the percentage of allergic ($n = 79$) and non-allergic ($n = 54$) 3 years old children and its change during the 4-year follow-up. After 4 years, 54% ($n = 29$) of previously non-allergic children became sensitized. Table 1 describes SPT results in non-allergic children ($n = 54$) at the age of 3 years and at follow-up visits. At the second visit, the most important allergen is house dust mite (20

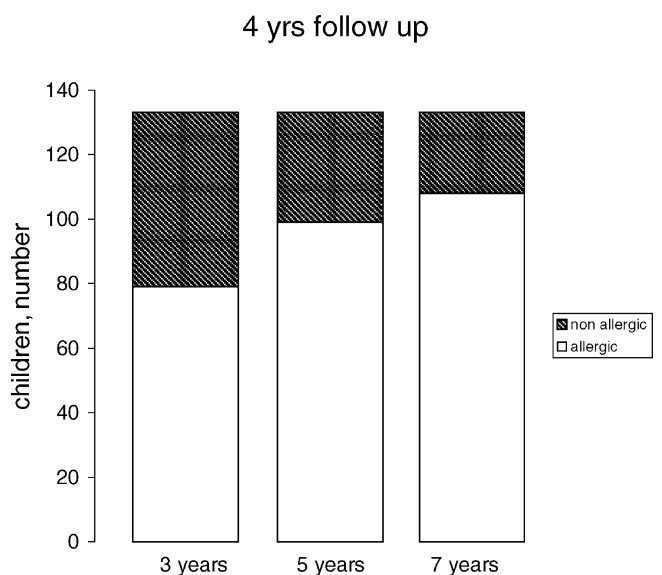


Fig. 1. Follow-up of children 3 years old age at first visit. After 4 years only 25 of them were non allergic.

Table 1

SPT sensitization for each allergen in non allergic children ($n = 54$) at the age of 3 years and at follow-up visits. After 4 years 54% ($n = 29$) of were allergic

Allergen	At 3 years	At 5 years	At 7 years
HDM	0	20	37
Dog	0	2	2
Cat	0	4	9
<i>Alternaria</i>	0	2	6
<i>Parietaria</i>	0	6	20
Grass	0	7	19
Olive	0	9	15

HDM: house dust mite.

children), surprisingly the second allergen is olive tree (9 children), other allergens are pollens (grasses and *Parietaria*) and cat. At the third visit, *Dermatophagoides* remain the most relevant allergen (37 children) followed by pollens (20 sensitized to *Parietaria*, 19 to grasses, and 15 to olive tree respectively). Nine children were sensitized to cat and two only to dog. It is noteworthy that 25 (46%) children remained non-allergic.

3.2. Allergic children, first visits

When considering only allergic children ($n = 271$), Fig. 2 describes mono-polysensitization distribution during the follow-up. At the age of 11 polysensitization became predominant.

3.3. Allergic children, follow-up

Fig. 3A–C describes sensitization distribution during the follow-up period in the three groups. Fig. 3A concerns the first group: *Dermatophagoides* are the most important allergen without significant difference during the three visits (Tables 2 and 3). Grasses, *Parietaria*, and cat significantly increase. It is of note that olive tree is the second aller-

Table 2

McNemar test for significance between first and final visit SPT results for different allergens in the three studied groups

Allergen	3 years vs. 7 years	7 years vs. 11 years	11 years vs. 15 years
HDM	NS	NS	NS
Dog	$P = 0.93$	$P = 0.37$	$P = 0.57$
Cat	$P = 0.014$	$P = 0.011$	$P = 0.37$
<i>Alternaria</i>	$P = 0.57$	$P = 0.63$	$P = 0.93$
<i>Parietaria</i>	$P = 0.0005$	$P = 0.19$	$P = 0.22$
Grass	$P = 0.002$	$P = 0.0002$	$P = 0.80$
Olive	NS	$P = 0.002$	NS

Table 3

Sensitization score in allergic subjects in the three different age groups during the 4 years follow-up period

Age groups (years)	U Mann–Whitney	Median (upper–lower quartiles)
3 vs. 5	$P = 0.0004$	1 (1–1)
5 vs. 7	$P = 0.04$	1 (2–1)
3 vs. 7	$P = 0.0001$	2 (3–1)
7 vs. 9	$P = 0.03$	1 (2–1)
9 vs. 11	$P = 0.0004$	2 (2.7–1)
7 vs. 11	$P = 0.0001$	2.5 (4–1)
11 vs. 13	$P = 0.12$	2 (3–1)
13 vs. 15	$P = 0.28$	2 (3–1)
11 vs. 15	$P = 0.01$	2 (3–1.7)

gen at baseline: this might explain the absence of statistical significance after 4 years.

Dog allergy remains very low during the study period.

Fig. 3B concerns the second group: the distribution of sensitizations during the three visits. It is interestingly to note that the baseline distribution is very similar to the second visit in group I: all of the children were 7 years old. House dust mites are the most important cause of sensitization also in this group and do not vary on the time. It deserves attention the fact that the percentage of sensi-

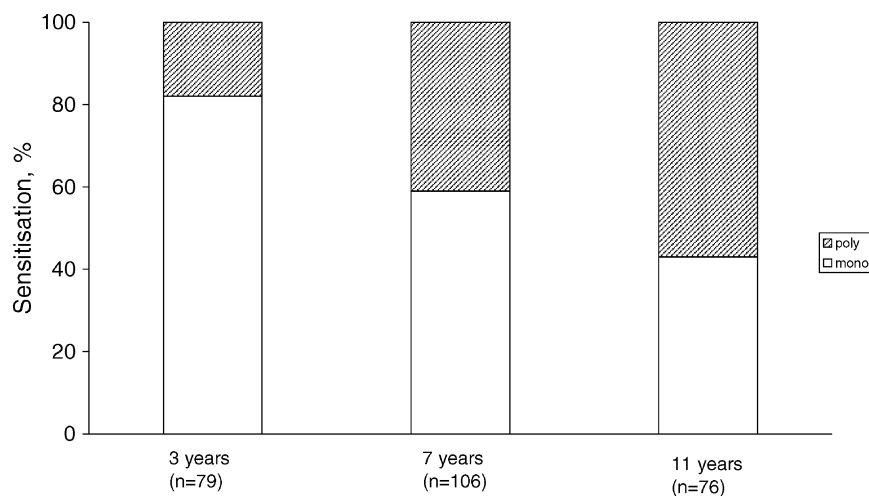


Fig. 2. Mono-polysensitization distribution at first visit in the three groups. Allergic children with polysensitization were more than monosensitized at the age of 11.

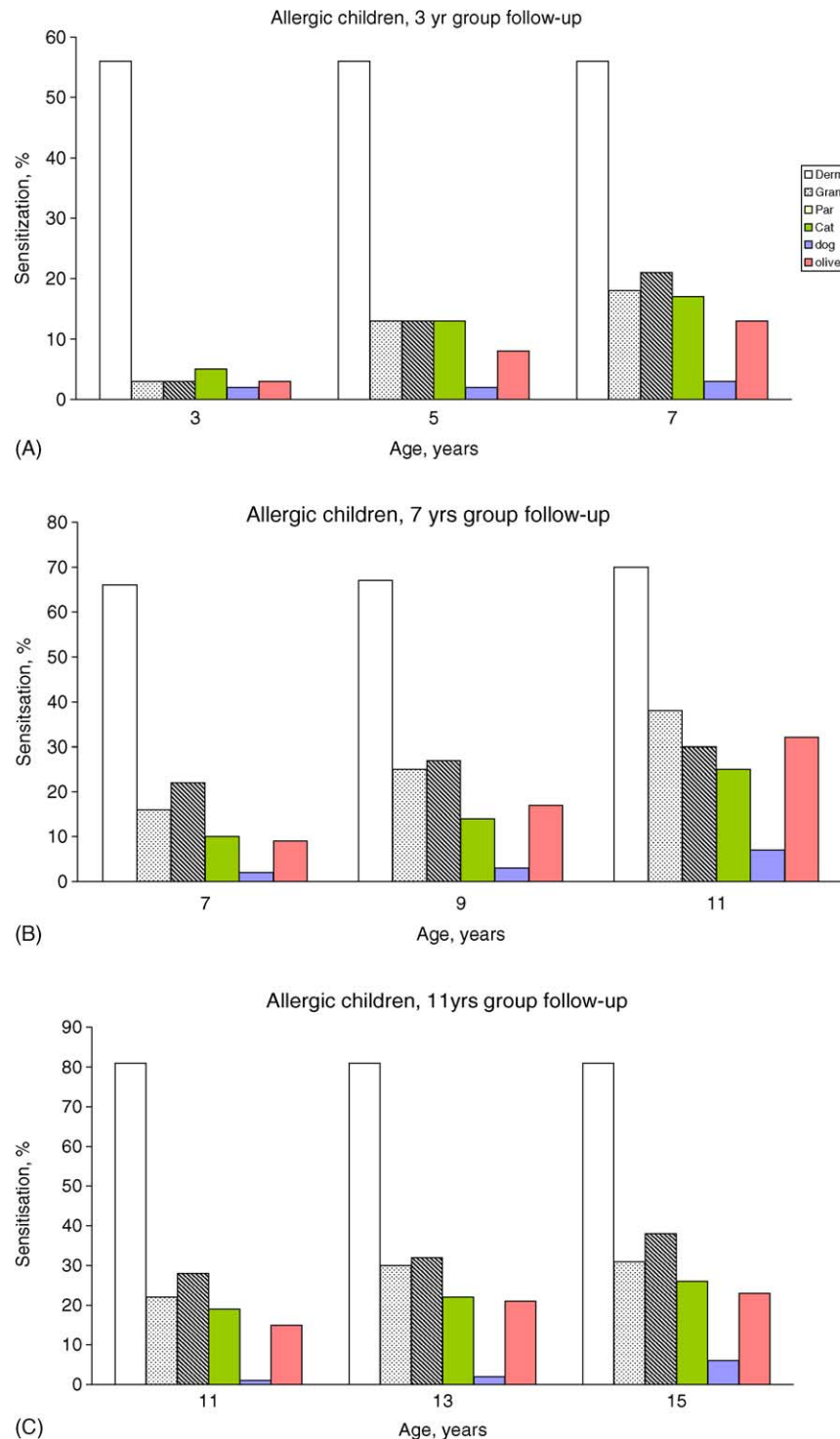


Fig. 3. Percentage distribution of more relevant SPT results in the 3 years (A), 7 years (B), 11 years (C) groups.

tized children to mites increases: approximately 70%. Instead, *Parietaria*, olive tree, and cat significantly increase after 4 years.

Fig. 3C concerns third group: house dust mites remain the most important allergen without variation during the study period, but the percentage of sensitized children progressively increases in this group: 80%. There is no varia-

tion among allergens during the study period as well as the percentage of polysensitized is higher than in other groups. Table 2 shows significant changes of sensitization distribution over the time. There was an increase in pollens and cat sensitization at the age range from 3 to 11 years. Table 3 shows sensitization score in allergic subjects in the three different age groups during the 4 years follow-up period.

4. Discussion

Asthma is a chronic inflammatory disease of airways characterized by a typical infiltrate, including T cells, eosinophils, and mast cells [13].

It is important to keep in mind that the immunopathology of asthma is similar in both allergic and non-allergic form [14]. Both variants share a common immunopathologic pattern mainly characterized by T helper 2 involvement and eosinophilic infiltration [15,16].

Even though asthma is a polyfactorial syndrome, IgE-mediated reaction is frequently involved in its immunopathophysiology, mainly in children [1,2].

This study highlights some important findings:

Firstly, it confirms the high percentage of asthmatic children showing sensitization and this increases with the age up to arrive at more than 80% of the older children.

Secondly, there is a typical natural history in the process of sensitization with high percentage of polysensitized children over the time.

Thirdly, there is a different behavior typical for each allergen, probably due to the antigenic characteristic of the single allergen.

Fourthly, the behavior of allergen sensitization seems to depend more on the age than on the period of symptom appearance.

As children referred to our clinic did not represent general population, we therefore limited analysis of allergic-non-allergic children distribution over the time only at 3 years old group. For this reason, the study was performed mainly on allergic children, at different ages (3–11 years).

We have to describe some characteristics of our study model. All studied children live in Liguria that is a region of Northern Italy characterized by a Mediterranean climate (warm winter and cool summer). So this temperate climate influences the pollen season of certain plants. *Parietaria* season is very prolonged as pollens may be detected since February to November, thus *Parietaria* may be considered as an almost perennial allergen. Grasses occur from April to June and from September to October [17]. Olive tree pollens are detectable for a very limited period (few weeks) at the end of May and early June [18].

About the first issue, it is well known that most of asthmatics are allergic in childhood and in adolescence [1,2]. This study confirms this evidence. House dust mites are the most important allergen involved in asthma pathogenesis and their prevalence increases with the age. In addition, *Dermatophagoides* remain the most relevant allergen also at 15 years.

Another important finding is that sensitization process shows a typical natural history: the trend to polysensitization. This study clearly demonstrates that most children become polysensitized over the time. Moreover, the age seems to be a critical factor in sensitization phenomenon. We did not find a substantial difference between children visited for the first time, i.e. at the onset of symptoms, and children

just symptomatic since 4 years. This finding might mean that allergy and asthma track two different ways: allergic events may precede clinical occurrence. Moreover, it is interesting to observe that some children are just polysensitized at the onset of asthma symptoms. In addition, there is a relationship between age and polysensitization independently on the age at asthma onset. In other words, sensitization seems to be a phenomenon partially independent on clinical events.

This issue deserves mention as it confirms previous findings. About the 50% of children is sensitized as reported by ourselves and other authors, but only half of them are affected from allergic disorders [6].

The third issue of this study constitutes new evidence, at our knowledge, at least for some allergen. In this survey, the most important allergens are: *Dermatophagoides*, *Parietaria*, grasses, olive tree, cat, and dog. Three of them (house dust mites, cat, and dog) are perennial allergens: i.e. present along the year. The remaining allergens are seasonal, being pollens: *Parietaria*, grasses, and olive tree.

If we analyze the distribution of sensitization in our cohort, we may observe very surprising findings. In the group of perennial allergen there is a very different behavior for mites in comparison with pets. Even though all of them are perennial allergens, mites are the most relevant allergen and their prevalence does not modify substantially over the time. On the contrary, cat and dog are less frequently cause of sensitization. However, there is further difference between them as cat allergy becomes significant over the time, whereas dog allergy remains quite rare. On the other hand, *Parietaria* allergy shows a trend similar to grasses. This finding is singular as *Parietaria* may be considered as a perennial allergen, whereas grasses are typical seasonal allergen. Olive tree is even more particular as this causes relevant sensitization, although its pollination period is very short.

These data, taken altogether, should be considered by the light of the immunologic feature of single allergens. It appears obvious that a conspicuous difference exists among allergens mainly concerning their period of presence in the environment. The most interesting allergens are mites, cat, and olive tree. Mite allergen is ubiquitous and is the most important cause of allergies in childhood as demonstrated also in the present study. Instead, dog allergen, even if it is perennial, is rarely cause of sensitization. This phenomenon may at least partially be explained by dog presence in houses that is quite rare (about 20–30%). Moreover, the same percentage of home presence corresponds for cat, but cat allergen shows peculiar characteristics. It is persistent, small (thus it easily penetrates into smaller airways), and overall detectable also in houses where it does not live. This finding is curious and is related to its characteristic to be transferred from one house to another by clothes. School is the ideal environment to allow this allergen passing as reported by various studies [19]. In this regard, it has been reported that most of cat-sensitized subjects do not own it at home. A Swedish study reported that 80% of children

sensitized to cat did not hold cats [20]. More recently, Turkish authors reported high percentage of sensitization to cat in comparison with very low percentage of its home presence (about 1%), but high levels of Fel d1 were detectable in many houses [21]. This phenomenon may be explained considering that cat allergen, unlike mite allergen, is persistently airborne in houses, the quantity of cat allergen inhaled is possibly higher than the quantity of mite allergen inhaled. On the other hand, there is evidence that cat allergen may protect from sensitization as numerous studies reported that the presence of cat since the birth may prevent allergies [22].

Finally, the fourth finding is noteworthy as highlights the concept that immune response to allergens is a phenomenon that is different from clinical features. From this point of view, we may consider that sensitization may be considered as a crucial risk factor for asthma onset. On the other hand, polysensitization existence at the asthma onset clearly testifies for a phenomenologic precedence of IgE-dependent events. It may be that chronic inflammation at respiratory mucosal level may predispose to asthma development.

In conclusion, the present study demonstrates that sensitization is very frequently associated with asthma and may precede asthma, and polysensitization is a common survey. In addition, allergens show different immunologic response depending on the type of T lymphocyte subsets involved. Further studies are warranted to investigate these immunologic aspects.

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