

Sensitization to inhalant allergens in wheezing infants is predictive of the development of infantile asthma

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Early recognition of infantile asthma in wheezing infants is a major problem for physicians. We investigated whether detection of early sensitization to inhalant allergens would be useful to identify those wheezing infants who are likely to develop asthma. A total of 67 infants (aged 1-25 months) hospitalized for a wheezing episode were initially tested for reactivity to inhalant allergens by both skin prick test and *in vitro* measurement of specific IgE antibodies (Phadiatop®). Thirty-seven of the infants were already considered to have infantile asthma, and 30 presented only their first or second wheezing episode when included in the study. All infants were followed for a mean period of 18 months. Seventeen (25%) infants, including seven infants initially not asthmatic, had positive prick test to *Dermatophagoides pteronyssinus* or to cat fur. All of these children were diagnosed as suffering from infantile asthma at the end of the follow-up. Thus, skin test positivity to inhalant allergens was significantly associated with the diagnosis of infantile asthma ($P < 0.05$) and could be considered to be predictive of the development of infantile asthma ($P < 0.03$). In contrast, Phadiatop was less sensitive than skin prick tests, and only five children had positive *in vitro* test results, suggesting that specific IgE may primarily bind to tissue mast cells before being detectable in serum. We concluded that sensitization to inhalant allergens may distinguish wheezing infants who develop asthma from those who do not, and that skin testing may assist the early diagnosis of asthma in wheezing infants.

C. Delacourt¹, D. Labbé², A. Vassault²,
D. Brunet-Langot¹, J. de Blic¹,
P. Scheinmann¹

¹ Service de Pneumo-allergologie infantile (Pr Scheinmann) and ² Service de Biochimie A (Pr Bailly), Hôpital des Enfants Malades, Paris, France

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Christophe Delacourt
Service du Professeur Scheinmann
Hôpital des Enfants Malades
149 rue de Sèvres
75015 Paris
France

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Wheezing illnesses in infants account for numerous hospitalizations and physician office visits. One of the major problems in managing these wheezing infants is to distinguish children who will develop asthma from those who will not. It is very important to recognize asthma as early as possible, not only to start adequate treatment and thus limit the morbidity, but, above all, to prevent mortality and the long-term pulmonary sequelae in adulthood (16). The delay in recognizing infantile asthma reflects the difficulty of diagnosis. The major role of viral infections as triggering factors for most of the wheezing episodes in infants increases this confusion (8, 11). The possibility of early diagnosis of infantile asthma by measuring the IgE response to common inhalant allergens has been poorly investigated. Moreover, previous work has not found any causal association between inhalant allergens and infantile asthma (19).

However, most asthma in childhood is associated with immediate hypersensitivity, especially to house-dust mite (14, 15), and the age at which the first episode occurs correlates well with the level of exposure to house-dust mite allergens (17). Therefore, we undertook this prospective study to determine whether the detection of early sensitization to inhalant allergens would be useful in distinguishing wheezing infants who develop infantile asthma from those who do not.

Material and methods

Patients

Between October 1990 and November 1991, 67 infants hospitalized in our pediatric department for bronchiolitis were initially tested for reactivity to pneumallergens by both skin prick test and *in vitro*

measurement of IgE antibodies. They were then followed prospectively for at least 1 year (mean $\pm$ SD: 18.6 ± 4.3 months) to assess the recurrence of wheezing episodes. All children were more than 2 years old by the end of the follow-up. The children were considered to have infantile asthma if they presented three or more separate wheezing episodes before 2 years of age, regardless of age of onset, evidence of atopy, and apparent precipitating cause of the wheeze (18). Alternative underlying causes of recurrent wheezing were excluded by an appropriate diagnostic investigation (2). For the purpose of this study, infants were classified into three groups according to their asthmatic status at the end of follow-up.

Group A ($n = 13$). This group comprised infants who presented only their first ($n = 11$) or second ($n = 2$) wheezing episode at the time of the tests, and who did not become asthmatic. None of these infants had another wheezing episode during the follow-up period.

Group B ($n = 17$). This group comprised infants who presented only their first ($n = 7$) or second ($n = 10$) wheezing episode at the time of the tests, and who subsequently had recurrent wheezing episodes and became asthmatic.

Group C ($n = 37$). This group comprised infants already considered to be asthmatic at the time of the tests.

Mean age, mean duration of follow-up, and history of familial atopy are reported in Table 1.

Our study design permitted us to answer two questions. First, by dividing infants into asthmatic (groups B and C) and nonasthmatic (group A), we determined whether positivity of skin tests to inhalant allergens in wheezing infants, whatever their

number of previous wheezing episodes, was associated with the diagnosis of infantile asthma. Second, by comparing group A to group B in an entirely prospective manner, we determined whether positivity of skin prick tests to inhalant allergens in wheezing infants who presented only their first or second wheezing episode was predictive of the development of infantile asthma.

Methods

Skin prick tests with disposable polymethacrylate needles (Stallerpoint®) were done in the morning according to a standard method (3), always by the same investigator (D.B.), in the absence of antihistaminic treatment. Standardized cat and *Dermatophagoides pteronyssinus* extracts (100 index of reactivity (biologic unit) per ml (10)) were purchased from Laboratoire des Stallergènes (Fresnes, France). Histamine hydrochloride (1.0 mg/ml) and codeine phosphate (9%) (Laboratoire des Stallergènes) were used as positive controls, and a glycerol solution (50%) (Laboratoire des Stallergènes) as negative control. A positive immediate reaction was recorded if the mean wheal diameter was ≥ 2 mm larger than that of the negative control.

Total IgE and Phadiatop® (Pharmacia Diagnostics, Uppsala, Sweden) were measured by the CAP system (Pharmacia Diagnostics). This system has been previously described in detail (16). Briefly, the immunoassay takes place within the Immunocap. It consists of a small capsule filled with a solid phase consisting of a cellulose derivative on which either antibodies against IgE (for total IgE measurements) or a balanced mixture of the most relevant allergens (for Phadiatop) are covalently bound. The binding capacity is increased by the three-dimensional structure of this solid phase. The sensitivity and specificity of this system are very high (4). Total serum IgE

Table 1. Specific IgE response to inhalant allergens in wheezing infants (infants classified into three groups according to number of wheezing episodes before inclusion and final asthmatic status)

No. of wheezing episodes on inclusion		<i>n</i>	Familial history of atopy	Initial age (months)	Follow-up (months)	Skin tests	Phadiatop
<3 and	Subsequently no recurrent wheezing (Group A)	13	Yes: 4 (31%) No: 9 (69%)	6.0±6.1	19.6±4.5	13 Neg. (100%) 0 Pos. (0%)	13 Neg. (100%) 0 Pos. (0%)
	Recurrent wheezing (Group B)	17	Yes: 5 (29%) No: 12 (71%)	9.6±6.3	20.5±3.7	10 Neg. (59%) 7 Pos. (41%)	14 Neg (82%) 3 Pos. (18%)
	≥ 3 (Group C)	37	Yes: 14 (38%) No: 23 (62%)	14.3±6.4	17.4±4.3	27 Neg. (73%) 10 Pos. (27%)	35 Neg (95%) 2 Pos. (5%)
	Total	67	Yes: 23 (34%) No: 44 (66%)	11.5±7.1	18.6±4.3	50 Neg (75%) 17 Pos. (25%)	62 Neg. (93%) 5 Pos. (7%)

is expressed in kilounits per liter (kUI/l). Values were considered to be elevated if they were ≥ 15 kUI/l under 6 months old, ≥ 20 kUI/l under 12 months, or ≥ 30 kUI/l under 24 months.

Statistical analysis

Contingency tables were analyzed by the chi-square test with the continuity correction method. A value of $P < 0.05$ was considered to be significant.

Results

Diagnosis of infantile asthma

By the end of the follow-up, 54/67 infants had presented three or more separate episodes of wheezing before 2 years of age and were considered to have infantile asthma, other causes of recurrent wheezing in infancy having been excluded. Fourteen of these 54 children were followed up to 3 years of age or more (mean age: 41.2 ± 2.7 months); all continued to have recurrent episodes of wheezing, with frequent nocturnal attacks and good response to bronchodilators, and could therefore be considered to have childhood asthma (2).

Skin test reactivity

No false positive reactions were observed with negative controls. The mean wheal diameter to histamine was 1.8 ± 1.0 mm. Sixteen of the 67 infants (23.9%) had a weak reactivity to histamine (wheal diameter less than 2 mm). Thirteen of these 16 patients were under 12 months old. The mean wheal diameter to codeine was 2.3 ± 1.3 mm. Only 10/67 children (14.9%) had a wheal diameter to codeine less than 2 mm. Eight of these 10 patients were under 12 months old. Seven children were hyporeactive to both histamine and codeine.

Allergenic skin prick tests

Seventeen of the 67 infants (25.4%) had positive allergenic tests; none of these children belonged to group A (Table 1). Thus, skin test positivity to inhalant allergens was significantly associated with the diagnosis of infantile asthma ($P < 0.05$). Among the 30 infants initially not asthmatic (groups A and B), seven had positive skin tests and became asthmatic. Positivity of allergenic test results was therefore significantly associated with development of infantile asthma ($P < 0.03$). Among group B infants, there was no difference in skin test positivity between those who presented their first wheezing episode and those who presented their second one at the time of study entry: positive allergenic skin tests were found in 3/7 infants (43%) with first episode and in 4/10 infants

(40%) with second episode. Skin prick tests were positive to *D. pteronyssinus* in 14/17 infants with positive tests and to cat fur in five. The mean wheal diameter of positive tests was 3.1 ± 2.0 mm (range 2–10).

Influence of age on skin test positivity

The fact that the mean age for group C was significantly higher than for groups A or B could have influenced the prevalence of allergic sensitization when the three groups were divided into asthmatic and nonasthmatic. However, this influence could be ruled out by showing that positivity of allergenic skin tests was not related to the age of infants. Ten of the 17 asthmatic infants with positive skin tests were under 12 months old, as compared with 34/50 infants with negative tests ($P = 0.49$). The mean age of these 17 asthmatic infants was 13.1 ± 7.7 months, not significantly differing from the mean age of those with negative skin tests, 12.7 ± 6.2 months (Fig. 1). Furthermore, the wheal size of positive tests was not significantly related to the age of infants (Fig. 2).

Total serum IgE antibodies

The percentage of infants with elevated total serum IgE was not significantly different among the three groups: total serum IgE was elevated in 3/13 group A children (23.1%), in 7/17 group B children (41.2%), and in 15/37 group C children (40.5%).

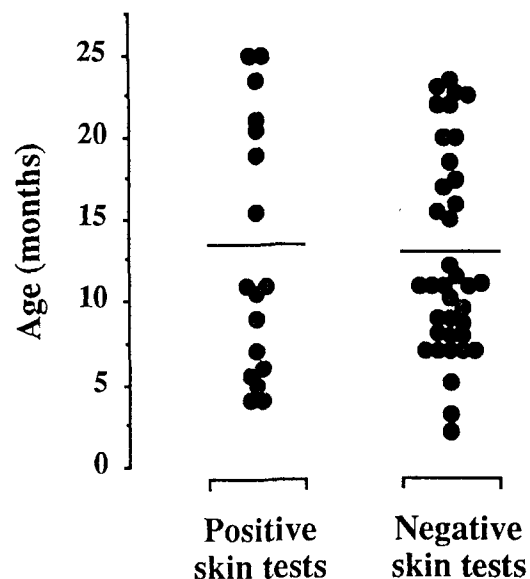


Fig. 1. Individual and mean ages in asthmatic infants with positive or negative skin tests to inhalant allergens.

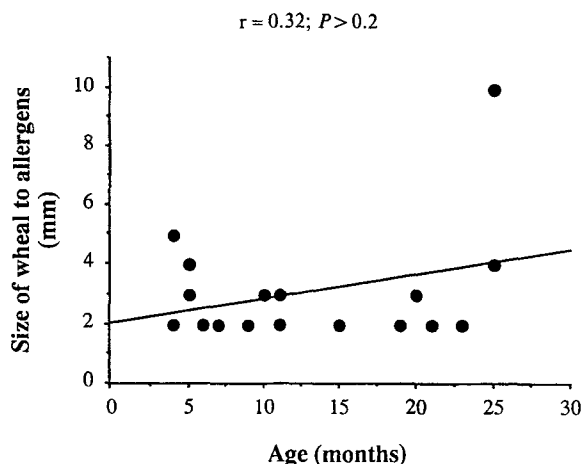


Fig. 2. Relationship between age and size of wheal to inhalant allergens in wheezing infants with positive skin prick test ($n = 17$).

Phadiatop

Five (three in group B and two in group C) of the 67 children had a positive *in vitro* test result (Table 1). Two of these five children had negative allergenic skin tests.

Discussion

Skin tests are a valuable tool in the diagnosis of immediate-type hypersensitivity. Prick tests can be easily done in infants, although the relative hypo-reactivity of infant skin must be taken into account (10). Nevertheless, there are wide variations in measurement and interpretation of skin test results. In particular, some investigators prefer to record the allergen-induced wheal size in infants as a ratio to that induced by positive control solutions (10). However, this method of recording depends on the choice of the positive control solution, and our results show that reactivity to histamine was lower than that to codeine phosphate. Moreover, a simple calculation shows that our conclusions do not depend on the scoring system: considering as positive an allergen-induced wheal size $> 75\%$ of that elicited by the codeine phosphate solution would have recognized 13 positive skin tests in our population (four in group B and nine in group C); on the other hand, a positive cutoff determined as a wheal size $> 75\%$ of that elicited by the histamine solution would have recognized 18 positive skin tests (seven in group B and 11 in group C), including the 17 recognized as positive by our scoring system. Thus, none of the group A children had positive skin test results under either method of recording.

Despite recent evidence from a prospective study suggesting that high-level exposure to house-dust mite allergens within the first 2 years of life may be

an important determinant of both sensitization to and risk of asthma (17), there are still few data available for infants on the association between inhalant skin test positivity and development of infantile asthma. Furthermore, previous work has suggested no relationship between sensitization to inhalant allergens and development of asthma within the first 20 months of life (19). However, the same authors reported in another study that 26% of asthmatic infants less than 2 years of age had positive skin test results to *D. pteronyssinus* (20). In our study, the rate of positive skin tests in asthmatic infants (groups B and C) was 26% to *D. pteronyssinus* and 9% to cat fur, and our results increase the evidence that sensitization to inhalant allergens is significantly associated with asthma in infants. Moreover, the sensitization preceded the diagnosis of asthma in seven wheezing infants and could therefore be considered to be a significant predictive factor of development of infantile asthma in these wheezing infants. If we take together the results of both allergenic skin tests and Phadiatop, the sensitization to inhalant allergens could be detected in 19 of the asthmatic infants (35.2%). Therefore, our data suggest that immediate hypersensitivity may be a factor causing lung inflammation and recurrent wheezing in infants, even if most wheezing episodes under the age of 2 years are probably due to viral infections (8).

There are a large number of mechanisms and risk factors underlying the likelihood of recurrent wheeze in infancy (7). In particular, the level of responsiveness to histamine in normal infants was found to be related to the presence or absence of a family history of asthma, suggesting that the initial level of airway responsiveness may be genetically determined (21). The level of airway responsiveness in early infancy may be further enhanced by parental smoking (21). However, the relation of this initial level of airway responsiveness to respiratory problems is still under debate, and a recent study has shown that bronchial responsiveness to histamine is independent of lower respiratory tract symptoms including wheezing (5). The role of inhaled allergens in the pathogenesis of wheezing in infants is also controversial. Although allergy is known to play a major role in the pathogenesis of childhood asthma (13), its role in infantile wheezing is often considered to be unimportant (12, 13), and skin testing is not considered to be a routine diagnostic procedure in wheezing infants (12). However, in contrast to previous conclusions (22), our findings imply that skin test reactivity to inhaled allergens is clinically relevant and that acquisition of inhalant sensitivity during infancy may predate the development of asthma not only later in childhood, but also as early as in the first 2 years of life.

Once the specificity and clinical correlation of

Immediate skin testing to inhalant allergens in infancy have been established, several major clinical applications arise. First, skin testing may be routinely used for wheezing infants. Positive allergenic skin tests may constitute a strong argument in consideration of diagnosis of asthma. Second, the therapeutic significance of early identification of asthma in wheezing infants relates to both avoidance of the relevant allergens and the use of anti-inflammatory drugs. Third, taken with the evidence that wheezing episodes are favored by atopy (1, 9), our results showing that sensitization to inhalant allergens is associated with the development of asthma in wheezing infants suggest that the reduction of mite exposure and other predisposing environmental factors (1) should be proposed before the first wheezing episode in at-risk infants for prevention of the development of asthma.

Finally, skin testing appears to be much more sensitive than Phadiatop in infants. Indeed, only five infants had positive Phadiatop results. A previous study performed with older children and adults found an excellent correlation between CAP and skin tests (4). However, very few data are available on the correlation between skin tests and RAST for sensitization to inhalant allergens in infants. Foucard found a weak correlation between these two tests for infants under 36 months: skin tests to various inhalant allergens were positive in 37% of wheezing infants, while only 18% of RAST tests were positive (6). This higher sensitivity of skin tests for infants suggests that specific IgE may primarily bind to tissue mast cells before being identifiable in serum.

In conclusion, our study shows that sensitization to inhalant allergens not only is associated with the diagnosis of asthma in infants, but also is predictive of development of asthma in wheezing infants. Skin test positivity may be present from the first wheezing episode, suggesting a pathogenic role of immediate hypersensitivity in the development of infantile asthma.

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