

Dynamic changes in sensitization to specific aeroallergens in children raised in a desert environment

D. A. Stern, I. C. Lohman, A. L. Wright, L. M. Taussig, F. D. Martinez and M. Halonen

The Arizona Respiratory Center and The Departments of Pharmacology and Pediatrics, The University of Arizona HSC, Tucson, AZ, USA

Summary

Background Allergen skin test reactivity and total serum IgE are objective measures used to characterize and help diagnose allergic diseases. Cross-sectional studies have shown that overall aeroallergen skin test reactivity increases throughout childhood. However, little attention has been paid to whether individual aeroallergen remittance occurs, which could distort or mask relationships to disease.

Objective To access the incidence and remittance of skin test reactions to individual allergens in children aged 6–11 years.

Methods Longitudinal sensitization to six aeroallergens and total IgE were assessed in 828 children raised in the semi-arid US southwest at ages 6 and 11 years.

Results New sensitization (to any allergen) between 6 and 11 years occurred in 30.2% of children compared with 39.7% before age 6 years. The rate of complete remittance from positive to negative between ages 6 and 11 years was 8.2%, and total IgE at age 6 years was not predictive. Remittance rates for individual allergens were high and variable (19–49%). The perennial allergens Bermuda and *Alternaria* were early sensitizers and had low remittance rates. Early sensitization to the four seasonal allergens was less common and more subject to remittance with the bulk of sensitization occurring between 6 and 11 years.

Conclusion This study shows that sensitization to individual aeroallergens in childhood is dynamic and indicates the limitation of single point assessment of skin test reactivity.

Keywords aeroallergen, allergy, *Alternaria*, atopy, children, desert, IgE, longitudinal, skin test

Submitted 31 July 2003; revised 20 September 2003; accepted 7 July 2004

Introduction

Local aeroallergens induce specific IgE synthesis to varying degrees among individuals in a given environment and the mast cell-sensitizing activity of this IgE can be assessed by immediate skin test reactivity. Immediate responses to skin prick tests (SPTs) are well established as diagnostic aids for the assessment of the allergen-specific basis for allergic manifestations. Nevertheless, the relationship is not invariant and measures of attributable risk examined in recent studies point toward less than half of allergic diseases being associated with risk assessed by positive skin tests [1, 2]. Whether assessment of allergen skin test reactivity at a single point in time is an adequate assessment of sensitization depends on the timing of incidence and remittance of reactivity to a given allergen and the relation of that pattern to symptoms. Cross-sectional data have suggested that the age at which sensitization is acquired is an important aspect of its relation to disease [3, 4], but few data are available documenting the longitudinal pattern of skin test reactivity

to individual aeroallergens, especially in children. An implicit assumption is that sensitization precedes development of symptoms. However, in one recent study that carefully documented the patterns of skin test reactivity and symptoms, the development of skin test reactivity after the development of symptoms occurred in approximately 25% of children who gained the label of seasonal allergic rhinitis before the age of 7 years [5]. Such data suggest that although sensitization is strongly associated with exacerbation of allergic symptoms, its causal role in the development of allergic disease is less clear.

Development and loss of reactivity has been noted to vary by allergen. Reactivity to food allergens can be evident in infancy and often disappears in early childhood [6]. However, skin test responses to aeroallergens are usually considered as rare in the first year of life but prevalence increases shortly thereafter [5] and increases steadily into at least the third decade, followed by decreases thereafter [7]. Remittance in childhood is assumed to be rare. Indeed, in a recent study, results from children showing skin test remission in the first 7 years were dismissed as spurious and were excluded from further analysis [5].

If individual allergens show different age-related sensitization patterns and especially if they show differences in

Correspondence: Marilyn Halonen, Arizona Respiratory Center, University of Arizona HSC, Tucson, AZ 85724, USA.
E-mail: mhalonen@arc.arizona.edu

remittance rates, the age-related pattern of sensitization to specific allergens within an individual might be more important than a single point determination of sensitization in assessing relation to risk for disease. Thus, prior to assessments of longitudinal patterns of allergic disease in relation to longitudinal patterns of skin test reactivity, we thought it is important first to establish the longitudinal skin test patterns in relation to age for the individual common local aeroallergens in a general population of children in the Tucson Children's Respiratory Study. We also sought to document the changes in total IgE level in relation to changes in skin test reactivity.

Methods

Subjects

The subjects of this report are participants in a longitudinal prospective study of childhood respiratory health [8]. A total of 1246 infants, whose families were members of a health maintenance organization in Tucson, Arizona, were enrolled at birth between May 1980 and October 1984 in the Tucson Children's Respiratory Study. Detailed health questionnaires were completed at regular intervals. Total serum IgE determinations and allergy SPTs were performed at ages 6 and 11 years. The analyses of this study are limited to children who had SPTs at age 6 and/or age 11 years ($n = 828$) or, for most of this report, to children who were skin tested at both ages for the same six allergens ($n = 642$, matched aeroallergen group). To assess any influence of ethnicity, the children were divided into two groups based on parental ethnicity: those with two Hispanic parents (11.8%) and those with at least one Anglo parent (81.6%). The remaining children of non-White and other mixed ethnicities were not included in the ethnicity analyses because of low subject number ($n = 54$). Informed consent was obtained from parents of participating subjects, and the study was approved by the Institutional Review Board of the University of Arizona.

Serum immunoglobulin E levels

Serum IgE levels were assayed by Phadebas radioimmunosorbent test using commercially available kits (Pharmacia Diagnostics, Piscataway, NJ, USA) as previously described [9]. At ages 6 and 11 years, peripheral blood samples for total serum IgE determinations were drawn from participating children ($n = 532$ and 600, respectively). For the samples within each time-point, IgE levels were unrelated to collection age. All samples were assayed in duplicate and results expressed as IU/mL.

Allergy skin prick tests

At age 6 years, extracts of seven common aeroallergens in the Tucson area and diluent were obtained from Hollister-Stier Laboratories (Everett, WA, USA) including: house dust mix (1:10 w/v), *Alternaria alternata* (1:100 w/v), Bermuda grass (*Cynodon dactylon*, 1:20 w/v), careless weed (*Amaranthus palmeri*, 1:20 w/v), and olive (*Olea europaea*), mesquite (*Prosopis glandulosa*) and mulberry trees (*Morus alba*) (1:20 w/v). Allergy SPTs were performed at age 6 years in 761

children (except mulberry tree antigen, which was applied to 731 subjects). Testing to the same allergens from the same supplier was repeated at age 11 years in 709 children, except that testing with house dust mix was discontinued after 96 subjects. Cat hair (10 000 BAU/mL) and *Dermatophagoides farinae* (30 000 AU/mL) were added to the testing at age 11 years and applied to 626 children. Children tested to the same allergens at ages 6 and 11 years (*Alternaria*, Bermuda grass, careless weed and olive, mesquite and mulberry tree allergens) served as a matched aeroallergen group of 642 subjects. All tests were read at 20 min and the sizes of the weals elicited by each allergen were recorded as the sum of the 2 diameters at right angles to each other (mm). Weal sizes of 3 mm or more after subtraction of diluent control size were considered positive.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for UNIX (SPSS Inc., Chicago, IL, USA), version 6. Total serum IgE values were log-normally distributed and the results expressed as geometric mean IgE (IU/mL). Incidences per 5-year period were calculated for the two age periods 1–6 and 6–11 years. Assuming no development of skin test reactivity to aeroallergens in the first year of life, the average time span for the skin-tested children was 5.3 years for the first period and 4.6 years for the second period. These spans were rounded to 5 years each for comparison purposes. A P -value < 0.05 (two-tailed) was considered statistically significant for all tests except in the case of multiple comparisons, for which a Bonferroni P -value was calculated.

Results

Prevalence of positive skin test reactivity at ages 6 and 11 years

Immediate skin test responsiveness to aeroallergens was common in the children of this study who were born and raised in the semiarid southwestern US environment of Tucson, Arizona. At age 6 years, 38.6% of the 761 children skin tested had a positive skin test reaction to at least one of the seven local aeroallergens. At age 11 years, prevalence of skin test reactivity was 58.1% in 709 children tested with eight allergens. For the group of 642 children with the same six skin tests applied in both years (referred to as the matched aeroallergen group), prevalence was 39.7% for positive skin tests at age 6 years and 54.6% at age 11 years. Of children who were skin test negative at age 6 years, 30.2% (117 of 387) became skin test positive by age 11 years. Thus, the acquisition of positive skin test reactivity status at age 11 years for children skin test negative at age 6 years was about 80% of that for acquisition during the age period before 6 years. Of the children who were skin test positive to at least one allergen at age 6 years, 91.7% (234 of 255) were also positive at age 11 years.

Changes with age in the number of positive skin tests for the matched aeroallergen group ($n = 642$) can be seen in Table 1. Overall, the prevalence of monosensitization

(sensitization to one allergen) was similar at ages 6 and 11 years (115 (17.9%) and 112 (17.4%), respectively). However, this similarity did not include many of the same subjects: at age 11 years, new monosensitization was common (54%, 61 of 112 children) and this increase was offset in part by age 6 years monosensitized individuals who remitted (12 of 115, 10.4%) but also by children moving from single (at age 6 years) to multiple sensitization at age 11 years (61 of 115, 53.5%), leaving only 42 who remained monosensitized at both ages. The prevalence of two positive tests increased by 21% (from 8.6% to 10.4%) and the occurrence of three to four and five to six positive tests approximately doubled by age 11 years. Nevertheless, while the number of sensitizing allergens increased for some subjects, the number decreased for others. The percent of children remitting reactivity to one or more allergens was greatest among those with the most skin tests (48.4% (15 of 31) of subjects in five to six positive skin test group).

Relation of longitudinal change in skin test reactivity to total serum immunoglobulin E

Geometric mean total serum IgE levels increased significantly from 36.8 IU/mL (95% confidence interval (CI) = 31.1–43.7) at age 6 years to 62.3 IU/mL (95% CI = 53.0–73.3) at age 11 years, $P < 0.001$. Children who completely remitted in skin test reactivity between ages 6 and 11 years were compared with those with persistent reactivity (either positive or negative) and those who gained reactivity (to any allergen) between ages 6 and 11 years. Table 2 shows that the skin test

remitting and persistent groups had equivalent total IgE levels at age 6 years but differed by age 11 years, with the persistent group increasing approximately 2-fold. The remitting group did not decrease in total IgE, however, but instead stayed at a plateau level. Subjects who developed new reactivity at age 11 years had higher IgE levels at age 6 years than subjects who remained skin test negative but lower than the two groups described above (who were already skin test positive at age 6 years). The newly reactive group showed a similar percent increase in IgE levels with age to the persistent group. The persistently negative group did not increase in IgE level between 6 and 11 years.

Incidence and remittance of individual allergen responses during two age periods

Although the age span of the early period (0–6 years) is not precisely equivalent in length to the 5-year later period (6–11 years), it is well documented that little to no skin test reactivity to aeroallergens is detected in the first year of life [6, 10]. Thus, for comparing incidences, the two age periods are considered roughly equivalent in length, providing two 5-year incidence rates (Figs 1a and b). The rank order of 5-year incidence rates for the individual allergens during the first period from highest to lowest was Bermuda grass > *Alternaria* > olive > careless weed > mesquite > mulberry. The rank order of incidence in the second period was strikingly different (Fig. 1b). Olive was the most frequent sensitizer and had an incidence rate about 2-fold greater than that of the early period. Mesquite and careless weed acquisition rates also approximately doubled those of the early period. In contrast, Bermuda was fourth and *Alternaria* fifth during the second period, and the incidence rates were lower for both of these antigens compared with the early period. Mulberry sensitization increased modestly in the second period but remained in sixth place (Fig. 1b).

Although not many subjects remitted from being skin test positive to completely skin test negative during the second period (8.2%), remittance rates for individual allergens were high, varying from 19% to 49% (Fig. 1c). The rank order for remittance was mulberry > mesquite > careless weed > olive > *Alternaria* > Bermuda, the reverse order of early sensitization. Remittance rates for mulberry, careless weed, mesquite and *Alternaria* did not vary by age 6 years weal size; children with larger weals were equally likely to remit completely compared with children with smaller weals. For

Table 1. Longitudinal change in number of positive skin tests*

Age 6 years skin test groups: number positive (n)†	Age 11 years skin test groups: number positive‡				
	0	1	2	3–4	5–6
	% of age 6 years skin test group				
0 (387)	69.8	15.8	5.4	7.2	1.8
1 (115)	10.4	36.5	16.5	24.3	12.2
2 (55)	14.5	5.5	20.0	36.4	23.6
3–4 (54)	1.9	7.4	25.9	40.7	24.1
5–6 (31)	0	6.5	6.5	35.5	51.6

*Analysis limited to subjects in the matched aeroallergen group ($n = 642$).

†Number of positive skin tests at age 6 years, n in each group.

‡Number of positive skin tests at age 11 years.

Table 2. Total serum IgE by skin test group at ages 6 and 11

Skin test groups*		Total serum IgE (IU/mL)			
		Age 6 years		Age 11 years	
Age 6 years	Age 11 years	N	Geometric mean (95% CI)	N	Geometric mean (95% CI)
Neg	Neg	198	15.9 (12.9–19.7)*	229	17.3 (13.8–21.6)*
Neg	Pos	82	26.3 (18.8–36.9)*	99	71.0 (51.7–97.4)
Pos	Neg	14	81.4 (41.3–160)	18	79.6 (43.3–146)
Pos	Pos	166	110 (88.6–137)	200	233 (195–279)*

Pos, positive for any matched allergen; Neg, negative for matched allergen; CI, confidence interval.

*Significantly different from all other groups at the same age, $P = 0.05$.

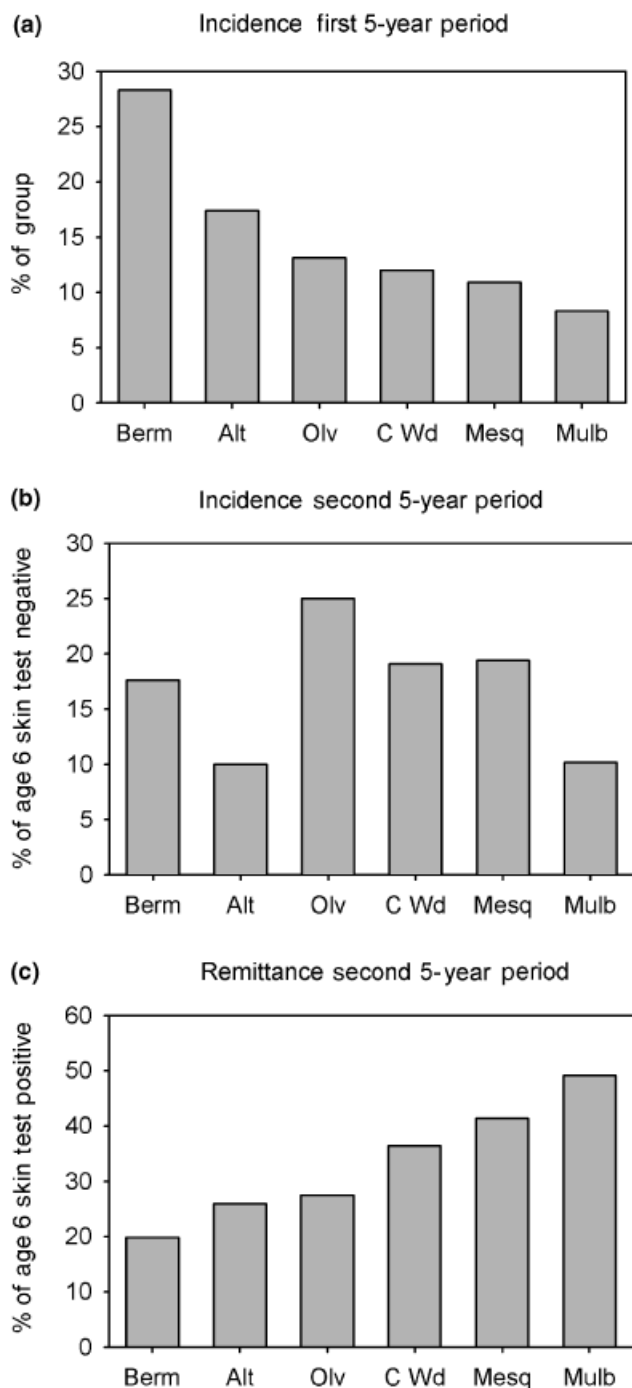


Fig. 1. Incidence and remittance of individual allergen immediate skin test responses in children. (a) Incidence for early 5-year period (ages 1–6 years); group $n = 642$. (b) Incidence for later 5-year period (ages 6–11 years); for Berm $n = 510$, Alt $n = 581$, Olv $n = 592$, C Wd $n = 611$, Mesq $n = 619$, Mulb $n = 594$. (c) Remittance by age 11 years of skin test positive reactions present at age 6 years; for Berm $n = 132$, Alt $n = 60$, Olv $n = 49$, C Wd $n = 30$, Mesq $n = 22$, Mulb $n = 25$. Berm, Bermuda grass; Alt, *Alternaria*; C Wd, careless weed; Mesq, mesquite and Mulb, mulberry.

Bermuda and olive allergens, weal sizes of 6–8 mm were similar in remittance to those of 3–5 mm. Only the largest weal sizes (>8 mm) were less likely to remit: for Bermuda, remittance for age 6 years weal sizes of 3–8 mm was 31.0% and for weal sizes >8 mm it was 10.2%, $P < 0.001$; for olive,

remittance for age 6 years weal sizes of 3–8 mm was 33.9% and for weal sizes >8 mm it was 9.1%, $P = 0.02$.

Prevalence of individual allergen responses

The prevalence of individual allergen responses at age 11 years resulting from the incidence and remittance rates described above are shown in Table 3. Despite a relatively low incidence rate of sensitization to Bermuda grass pollen between ages 6 and 11 years, responses to this allergen remained the most prevalent at age 11 years. *Alternaria* responses, however, fell in rank from second at age 6 years to fifth at age 11 years. Olive responses became more prevalent, moving in rank from third to second, and careless weed and mesquite also moved up in prevalence.

Although not included in the matched aeroallergen group, sensitization to house dust mix had the lowest prevalence of all allergens at age 6 years, 4.6% ($n = 761$). Similarly, of the 96 children tested to house dust mix at age 11 years, only 6.3% were positive. Prevalence of responses to *D. farinae* at age 11 years was low, 14.9% ($n = 626$), ranking sixth of eight allergens tested. Sensitization to cat hair at age 11 years was the lowest of all allergens, 5.1% ($n = 626$). There was no difference in sensitization to cat hair between those children with (3.1%, $n = 160$) vs. those without indoor cats (5.9%, $n = 455$), $P = 0.2$.

Prevalence by gender and ethnicity

Gender differences for sensitization to aeroallergens were relatively minor but reached a Bonferroni-corrected significance level ($P = 0.008$) for Bermuda and for any skin test at age 6 years only, with boys having increased reactivity over girls (Table 3). The rank order of individual allergen responses was similar by gender at both ages 6 and 11 years (Table 3). The prevalence of skin test reactivity in Hispanic children did not differ significantly from that in children with at least one Anglo parent at age 6 years (35.0% vs. 40.3%, respectively, $P = 0.4$) or age 11 years (45.0% vs. 55.9%, respectively, $P = 0.07$) in the matched aeroallergen group.

Contribution of persistent vs. new sensitization to prevalence at age 11 years

Figure 2 illustrates the contribution of persistent vs. new sensitization to age 11 years prevalence for each allergen. For Bermuda and *Alternaria*, subjects with persistent skin test reactivity made the major contributions to the age 11 years prevalence, whereas subjects with new sensitizations were the major contributors for the other four allergens.

Discussion

Immediate skin test reactivity to common environmental allergens provides a valuable aid to physicians in diagnosing and treating allergic conditions. Factors other than allergic symptoms, such as gender and age, have been shown to influence skin test reactivity prevalence [11, 12]. The study described herein extends our understanding of skin test reactivity by demonstrating the degree to which longitudinal

Table 3. Prevalence of individual skin tests at age 6 and 11 years for matched aeroallergen group and by gender

Allergen	% skin test positive at age 6 years				% skin test positive at age 11 years			
	All, <i>n</i> = 642	Boys, <i>n</i> = 322	Girls, <i>n</i> = 320	<i>P</i> *	All, <i>n</i> = 642	Boys, <i>n</i> = 322	Girls, <i>n</i> = 320	<i>P</i> *
Bermuda	28.3	33.2	23.4	0.006	35.4	39.8	30.9	0.02
<i>Alternaria</i>	17.5	20.5	14.4	0.04	21.2	24.8	17.5	0.02
Olive	13.1	14.9	11.3	0.2	31.3	35.7	26.9	0.02
Careless weed	12.0	14.0	10.0	0.1	24.6	28.0	21.3	0.05
Mesquite	10.9	13.7	8.2	0.03	23.8	25.5	22.2	0.3
Mulberry†	8.6	10.5	6.5	0.07	14.0	16.5	11.6	0.07
Any‡	39.7	45.0	34.4	0.006	54.7	58.7	50.6	0.04

**P*-value for *t*-test of boys and girls.

†At age 6 years, boys *n* = 313 and girls *n* = 306 for mulberry.

‡Positive to at least one of the six matched aeroallergens.

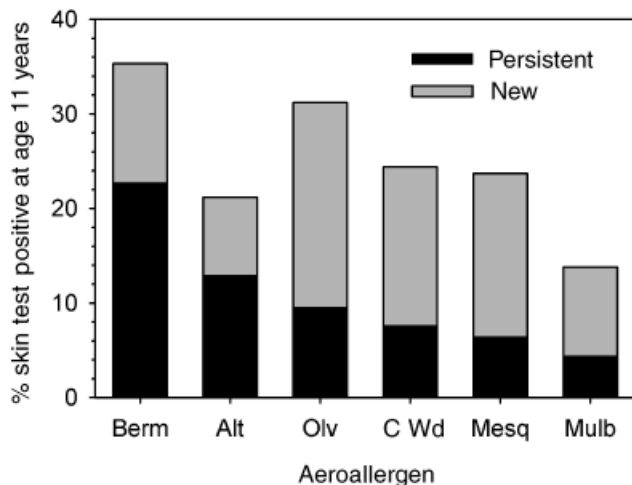


Fig. 2. Prevalence of persistent and new skin test responses for individual allergens at age 11 years. Persistent responses are those present at both ages 6 and 11 years. New responses are those negative at age 6 years and positive at age 11 years. Each percent skin test positive at age 11 years is the percent of *n* = 642. Allergen abbreviations as in Fig. 1.

variation in reactivity to individual aeroallergens occurs during childhood and by documenting variation in both incidence and remittance. The findings suggest that responses at one time-point in a given individual are not necessarily reflective of either future or past reactivity.

Although sensitization to foods is generally regarded as peaking and then waning during the first 1–2 years of life [5], a concept has emerged that aeroallergen sensitizations commence close to the second or third year of life and continue to increase or persist thereafter for many years [6]. Previous cross-sectional studies have reported age-related increases in prevalence of skin test responses through this age period and continuing into at least the third decade of life [11]. Considering aeroallergen skin test reactivity as a dichotomous variable (positive or negative), our study supports such a concept. The predicted age-related increase in skin test prevalence was indeed apparent from ages 6 to 11 years.

In contrast, examination of the skin test data for individual allergens shows that many dynamic changes occur, with both increase and loss of sensitization to the individual allergens. Skin test responses to specific allergens differed in acquisition rates during the second vs. the first 5-year period. New

sensitization to *Alternaria* and Bermuda was much greater in the first age period compared with the second, whereas the opposite was true for olive, mesquite and careless weed, with mulberry having similar rates during both periods. These last four allergens are considered more seasonal than Bermuda and *Alternaria* in this locale [13]. Early sensitization to these allergens occurred primarily in those children who also gained sensitivity to the perennial allergens. Thus, it appears that peak rates of acquisition to perennial allergens occur earlier in life and only children with a general increased susceptibility to becoming sensitized developed sensitization to the seasonal allergens by the age of 6 years.

At age 11 years, skin testing to house dust mix was replaced by testing to *D. farinae* because the low prevalence of positive responses to house dust mix at age 6 years may have indicated that house dust mix did not contain enough dust mite allergen to detect sensitization to dust mites. Indeed, using all available skin test data, the responses to house dust mix were examined to determine if they were due largely to *D. farinae*. Prevalence of *D. farinae* responses at age 11 years was 14.9% compared with 6.6% for house dust mix, but these data were obtained from separate groups of children and thus direct determination of whether the house dust mix positive children were all positive for *D. farinae* (or vice versa) at the same time-point was not possible. However, it appears that this is likely not the case in that of the 30 children positive to house dust mix at age 6 years and tested for *D. farinae* at age 11 years, only 10 (34.5%) were positive for *D. farinae* at age 11 years. This frequency was similar to those seen for children sensitized to the other allergens tested at age 6 years: response frequencies to *D. farinae* at age 11 years for children who were skin test negative to house dust mix at age 6 years but skin test positive to at least one of the other allergens ranged from 23.3% (for Bermuda) to 32.1% (for careless weed).

Skin test reactivity to each allergen showed large remittance rates during the 6–11-year age period. Bermuda (an allergen that varies in amount but is in the environment through all of the seasons) had the lowest remittance rate. Even for this antigen, 20% of children who were positive at age 6 years reverted to negative by age 11 years. Remittance rates of the various allergens were inversely related to the prevalence of individual allergen responses at age 6 years (see Figs 1a and c) and were unrelated to the simultaneous acquisition of new sensitization from ages 6 to 11 years (see Figs 1b and c). These data suggest that the prevalence at any one time-point is

controlled more by subject-related factors than by environmental levels of allergens.

The differing acquisition rates with age together with remittances in reactivity in those already positive at age 6 years led to a different rank order of prevalence by age 11 years. Despite a lower incidence in the second 5-year period, Bermuda remained the most prevalent sensitizer at age 11 years. In contrast, the *Alternaria* response prevalence fell behind three seasonal allergens and the response to olive became the second most prevalent behind Bermuda. These data emphasize that individual skin test responses at one point in time do not necessarily reflect the reactivity pattern that was present at another time, which likely has clinical implications for the use of skin test responsiveness in relation to contribution to or prediction of disease and that require further study.

That the incidence and remittance rates represent temporal changes (rather than variability in testing) is supported by the findings of a study by Barbee et al. [7], who assessed the reproducibility of the SPT reaction by testing 1387 subjects with Bermuda allergen in two skin areas simultaneously (and whose methods we have followed precisely). At the first site, 1057 subjects were skin test negative and 1020 were also negative at the second site (3.5% became positive, 'incidence' 37/1057) and, at the first site, 330 were skin test positive and 312 were also positive at the second site (5.5% became negative, 'remittance', 18/330). The incidence and remittance rates reported here are substantially greater than those occurring by simultaneous testing.

Regional differences in the spectrum of responses to specific aeroallergens have been documented. It is well established, for example, that house dust mite (HDM) is a major sensitizing allergen in many locales worldwide [14–16], although quite dramatic regional differences have been shown to occur for sensitization to this allergen and also to grasses and moulds among children living in environments that differ in relative humidity and temperature [4, 17–20]. The prevalence of reactivity to *D. farinae* was relatively low in our population compared with those from other locales [13]. The HDM has been reported to have an absolute survival requirement for a relative humidity of at least 50% [20]. Relative humidity is often less than this during the year in Tucson, although microenvironments within houses apparently allow pockets of infestation in at least some households [21]. Thus, the allergens typically limited to indoor rather than outdoor environments are not major sensitizing allergens in the Tucson area, possibly reflecting the more open-to-the-outdoor-environment lifestyle that occurs as a result of our year-round mild weather.

It was our expectation that mould sensitization would also have a low prevalence in our population, given our low relative humidity. However, responses to *Alternaria* proved to be prominent at age 6 years, second only to those invoked by Bermuda grass pollen. Apparently, moulds like *Alternaria* become more airborne in dry climates like that of the Tucson area [22–25]. Although it is possible that there are indoor microenvironments that foster mould growth, environmental studies indicate that the major source of indoor concentrations of this allergen is from outdoors [26–28]. The time for the greatest acquisition rate for this allergen was early in life, after which that rate fell dramatically. Thus, an early

susceptibility to sensitization that decreases with age occurs with this allergen despite its continued presence in the environment. Bermuda grass, a perennial or nearly perennial allergen in our environment, showed a pattern similar to that of *Alternaria*. The importance of this issue is emphasized in our own recent finding that age 6 years skin test reactivity to *Alternaria* was more reflective of the association with asthma diagnosed after age 6 years than was reactivity at age 11 years [4]. Studies by Peat et al. [3] also indicate that the age of sensitization is critically important in the degree of risk for allergic disease. Further studies are needed for other allergy-related syndromes and allergen sensitization patterns in this and other locales.

The positive skin test prevalences of 38.6% at age 6 years and 58.1% at age 11 years are much higher than the reported prevalence of approximately 18% for 6–11-year-old children tested with eight allergens at 64 sites throughout the US during the second (1976–1980) National Health and Nutrition Examination Survey [12] (see Fig. 1) but relatively similar to those of more recent studies in 8–11-year-old children in Australia (35–40%) [18] and in 13-year-old children in New Zealand (43.8%) [29]. These data suggest that allergen skin test reactivity is increasing in the general population in at least westernized societies. Separating time-related increases from regional or methodological differences is difficult; nevertheless, at least two studies have suggested that such increases in skin test reactivity have been occurring over (at least) the last few decades [30, 31].

Although skin test responses have the potential to be regulated by processes in addition to the amount of specific IgE present, the close association of total IgE to skin test reactivity is well known. Total serum IgE increased from ages 6 to 11 years for the group as a whole. However, in subjects who remained skin test negative, total IgE levels were equivalent at ages 6 and 11 years and were significantly lower than all other groups at both ages. Among those completely remitting responsiveness to skin tests between ages 6 and 11 years, IgE was not lower at age 6 years compared with those not remitting. However, the remitters differed from those consistently positive at age 11 years (who more than doubled their geometric mean IgE level). Thus, the relation between specific IgE contributing to skin test positivity and total IgE appear to be closely tied in a temporal sense. The data suggest that changes in total IgE appear to be concomitant with or follow but do not predict subsequent changes in skin test reactivity.

In summary, we have shown that children raised in a semi-arid region of the US southwest had relatively high rates of skin test prevalence that increased from ages 6 to 11 years. Boys had higher prevalence than girls had at age 6 years. Responses to perennial allergens were most prevalent at age 6 years, with Bermuda grass pollen in first place and *Alternaria* responses second, although the perennial indoor allergen, *D. farinae*, was not a major allergen in this locale. Despite an overall increase in skin test reactivity from ages 6 to 11 years, remittance rates for all individual allergens during this period were high, demonstrating a limitation of single time-point skin test data. Among those gaining skin test reactivity, Bermuda and *Alternaria* incidence rates were lower in the second 5-year period than in the first and support the concept that perennial allergens initiate sensitization earlier in life.

Those remaining skin test negative at ages 6 and 11 years had significantly lower IgE levels at both ages. The studies emphasize that skin test reactivity at more than one time-point during childhood together with IgE assessment provides a more complete characterization of allergen sensitization status in childhood.

Acknowledgements

The authors wish to thank the study nurses, Marilyn Lindell and Lydia de la Ossa, for performing the skin tests and Bruce Saul and Cathy Ward for data input and management. This study is supported by NIH grants HL14136, AI44697, HL56177.

References

- Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax* 1999; 54:268–72.
- Arshad SH, Tariq SM, Matthews S, Hakim E. Sensitization to common allergens and its association with allergic disorders at age 4 years: a whole population birth cohort study. *Pediatrics* 2001; 108:E33.
- Peat JK, Salome CM, Woolcock AJ. Longitudinal changes in atopy during a 4-year period: relation to bronchial hyperresponsiveness and respiratory symptoms in a population sample of Australian schoolchildren. *J Allergy Clin Immunol* 1990; 85 (Part 1):65–74.
- Halonen M, Stern DA, Wright AL, Taussig LM, Martinez FD. *Alternaria* as a major allergen for asthma in children raised in a desert environment. *Am J Respir Crit Care Med* 1997; 155: 1356–61.
- Kulig M, Klettke U, Wahn V, Forster J, Bauer CP, Wahn U. Development of seasonal allergic rhinitis during the first 7 years of life. *J Allergy Clin Immunol* 2000; 106:832–9.
- Kjellman NI, Björkstén B, Hattévig G, Falth-Magnusson K. Natural history of food allergy. *Ann Allergy* 1988; 61 (Part 2): 83–7.
- Barbee RA, Lebowitz MD, Thompson HC, Burrows B. Immediate skin-test reactivity in a general population sample. *Ann Intern Med* 1976; 84:129–33.
- Taussig LM, Wright AL, Morgan WJ, Harrison HR, Ray CG. The Tucson children's respiratory study. I. Design and implementation of a prospective study of acute and chronic respiratory illness in children. *Am J Epidemiol* 1989; 129:1219–31.
- Halonen M, Stern D, Lyle S, Wright A, Taussig L, Martinez FD. Relationship of total serum IgE levels in cord and 9-month sera of infants. *Clin Exp Allergy* 1991; 21:235–41.
- Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol* 1999; 103:1173–9.
- Gergen PJ, Turkeltaub PC, Kovar MG. The prevalence of allergic skin test reactivity to eight common aeroallergens in the U.S. population: results from the second national health and nutrition examination survey. *J Allergy Clin Immunol* 1987; 80:669–79.
- Gergen PJ, Turkeltaub PC. The association of individual allergen reactivity with respiratory disease in a national sample: data from the second national health and nutrition examination survey, 1976–80 (NHANES II). *J Allergy Clin Immunol* 1992; 90 (Part 1): 579–88.
- Thompson HC, Gundersen E, McNeely RA. Causes of respiratory allergy in Arizona. Part I. *Ariz Med* 1977; 34:387–8.
- Platts-Mills TAE. Dust mite allergens and asthma – a worldwide problem. *J Allergy Clin Immunol* 1989; 83:416–27.
- Lau S, Falkenhörst G, Weber A et al. High mite-allergen exposure increases the risk of sensitization in atopic children and young adults. *J Allergy Clin Immunol* 1989; 84 (Part 1):718–25.
- Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. *N Engl J Med* 1990; 323:502–7.
- Charpin D, Birnbaum J, Haddi E et al. Altitude and allergy to house-dust mites. A paradigm of the influence of environmental exposure on allergic sensitization. *Am Rev Respir Dis* 1991; 143 (Part 1):983–6.
- Peat JK, Tovey E, Mellis CM, Leeder SR, Woolcock AJ. Importance of house dust mite and *Alternaria* allergens in childhood asthma: an epidemiological study in two climatic regions of Australia. *Clin Exp Allergy* 1993; 23:812–20.
- Murray AB, Ferguson AC, Morrison BJ. Sensitization to house dust mites in different climatic areas. *J Allergy Clin Immunol* 1985; 76:108–12.
- Platts-Mills TA, Sporik R, Ingram JM, Honsinger R. Dog and cat allergens and asthma among school children in Los Alamos, New Mexico, USA: altitude 7200 feet. *Int Arch Allergy Immunol* 1995; 107:301–3.
- Arlian LG. Water balance and humidity requirements of house dust mites. *Exp Appl Acarol* 1992; 16:15–35.
- O'Rourke MK, Fiorentino L, Clark D, Ladd M, Rogan S, Carpenter J. Building characteristics and importance of house dust mite exposure in the Sonoran Desert, USA. *Proc Indoor Air* 1993; 4:155–60.
- Downs SH, Mitakakis TZ, Marks GB et al. Clinical importance of *Alternaria* exposure in children. *Am J Respir Crit Care Med* 2001; 164:455–9.
- Srisvastava AK, Wadhwani K. Dispersion and allergenic manifestations of *Alternaria* airspora. *Grana* 1992; 31:61–6.
- Sneller MR, Hayes HD, Pinnas JL. Frequency of airborne *Alternaria* spores in Tucson, Arizona over a 20-year period. *Ann Allergy* 1981; 46:30–3.
- Hjelmroos M. Relationship between airborne fungal spore presence and weather variables. *Cladosporium Alternaria* 1993; 32:40–7.
- Meldrum JR, O'Rourke MK, Boyer-Pfersdorf P, Stetzenback LD. Indoor residential mold concentrations as represented by spore and colony counts. *Proc Indoor Air* 1993; 4:189–94.
- Verhoeff AP, van Wijnen JH, Brunekreef B, Fischer P, van Reenen-Hoekstra ES, Samson RA. Presence of viable mould propagules in indoor air in relation to house damp and outdoor air. *Allergy* 1992; 47 (Part 1):83–91.
- Sears MR, Burrows B, Flannery EM, Herbison GP, Holdaway MD. Atopy in childhood. I. Gender and allergen related risks for development of hay fever and asthma. *Clin Exp Allergy* 1993; 23:941–8.
- Oryszczyn MP, Annesi I, Neukirch F, Dore MF, Kauffmann F. Longitudinal observations of serum IgE and skin prick test response. *Am J Respir Crit Care Med* 1995; 151 (Part 1):663–8.
- Barbee RA, Halonen M, Kaltenborn W, Lebowitz M, Burrows B. A longitudinal study of serum IgE in a community cohort: correlations with age, sex, smoking, and atopic status. *J Allergy Clin Immunol* 1987; 79:919–27.