Clin Exp Allergy 2005; **35**:70–74 doi:10.1111/j.1365-2222.2005.02142.x

Allergen skin weal/radioallergosorbent test relationship in childhood populations that differ in histamine skin reactivity: a multi-national survey

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Summary

Background Histamine skin reactivity (HSR, the dimension of the skin weal elicited by histamine 10 mg/mL) is a variable that differs in children from different European countries and increases over time in the same place (Italy).

Objective In this epidemiologic study, we investigated to what extent differences in HSR influence the relationship between positive allergen skin prick tests (ASPTs) and serum-specific IgE concentrations.

Methods Between October 2001 and February 2002, 591 unselected 9–10-year-old schoolchildren drawn from five small towns in central Poland (Starachowice), central Italy (Ronciglione, Guardea) and Libya (Al-Azyzia, near the Mediterranean sea and Samno, 900 km south of the coast) were analysed for histamine, common ASPT and for serum total and specific IgE.

Results HSR differed markedly in children from the three countries (Libya > Italy > Poland) whereas serum total IgE concentrations remained the same. The prevalence of children with measurable serum specific IgE ($\geqslant 0.35$ kU) or with a positive ASPT for five common allergens was high in Italy, lower in Poland and far lower in Libya. A 3-mm ASPT weal corresponded to a serum-specific IgE concentration that was two to threefold higher in children with low HSR compared with children with high HSR ($P = 0.008$).

Conclusion These findings suggest that HSR – a variable that differs in schoolchildren populations from the three countries studied – independently influences the results of ASPT and its influence should be considered when ASPT are assessed in international studies. The HSR differences found in the populations reported here probably reflect a complex, dynamic, environmental interaction that should be monitored in the different parts of the world.

Keywords allergen skin prick tests/RAST ratio, children, epidemiology, histamine skin reactivity
Submitted 19 March 2004; revised 27 September 2004; accepted 26 October 2004

Introduction

Allergen skin prick testing (ASPT) is the method of choice for the *in vivo* diagnosis of atopy. Over the past decades, efforts to study and standardize the methods, devices and allergenic extracts for use in this diagnostic procedure led to several official position papers on skin tests [1, 2]. The ASPT technique is nonetheless notoriously difficult to standardize [3–8] and the results depend on many factors. Some are linked to the conditions chosen for the test, for example the technique and device [9–13] site used for skin testing, time of day, season of the year [14, 15], potency of the extract [14, 16, 17] and method of reading [18–20]. Others relate to individual characteristics of the subject including age [21–23], sex [24], genetic predisposition [25], and the effect of changing or different life-styles [26, 27]. The results of ASPT also depend on total serum IgE [28] and histamine skin reactivity (HSR) [25, 29, 30]. The latter two factors may emerge as important confounding variables when populations from the same geographical setting are tested over time [31, 32] or populations living in distant and dissimilar countries are investigated at the same time [33–35]. We have recently shown that in comparable cohorts of age-matched children from the same area the prevalence of positive ASPT and skin reactivity to histamine (HSR, mean dimension of skin weal elicited by histamine 10 mg/mL) both increased over time (16 years) [32]. In another study, we found significantly lower histamine and allergen skin reactivity in unselected 9-year-old children from Poland than from Italy [36]. From both studies we concluded that HSR undergoes short-term changes; it probably comes under the influence of life-style or other environmental factors. Because the fundamental mediator released during

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the immediate skin response to allergen is histamine, any difference or change in HSR can alter the prevalence of positive ASPT.

To extend our epidemiological research and find out to what extent differences in HSR influence the relationship between positive ASPT and RAST, in this study we investigated new unstudied populations of unselected children from two countries with proven differences in HSR (Italy and Poland) and from a third country that differs markedly in industrialization and life-style (Libya). We compared HSR and atopy, namely skin reactivity to allergens and serum-specific IgE concentrations, in the three populations.

Materials and methods

Study populations

The population comprised all fourth-grade children attending schools in small semi-rural cities) in central Poland (Starachowice, 59 000 inhabitants), central Italy (Ronciglione, 30 000 inhabitants and Guardea, 10 000 inhabitants) and Libya (Al-Azizia, near the Mediterranean Sea, 76 000 inhabitants and Samno, 900 km from the sea at the border of the Sahara desert, 14 000 inhabitants). All studies were conducted between October 2001 and February 2002. Blood samples were obtained for 593 (83%) of the 713 children eligible in the five cities (technical problems prevented vein puncture in the 150 children from Legnica, Poland who were originally part of the study). Diplomatic and local authorities and parents gave their written informed consent for the children to take part in the study. The study was approved by the Ethical Committee of the Pediatric Clinic of Rome University 'La Sapienza'.

Skin prick tests

For 1 week before testing all children were asked to refrain from antihistamine medications and from inhaled or oral corticosteroids. When prick tested all participants denied the use of long-acting antihistamine preparations. Skin prick tests (SPTs) with two different concentrations of histamine were done in the left forearm: histamine 10 mg/mL on the inner side 3 cm distal to the elbow crease and histamine 1 mg/mL on the outer side 4 cm distal to the elbow crease. ASPTs were done in a predefined area on the volar side of the left forearm, with a space of at least 2.5 cm between each prick. According to the International Study of Asthma and Allergic disease in Childhood (ISAAC) protocol phase 2 [37] the following inhalant allergens panel were tested: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat hair, *Alternaria tenuis*, mixed grasses 1 (*Avena sativa*, *Hordeum vulgare*, *Secale cereale*, *Triticum sativum*), mixed grasses 2 (*Dactylis glomerata*, *Festuca pratensis*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis*), and mixed trees (*Betula verrucosa*, *Corylus avellana*, *Alnus glutinosa*). Negative controls, 50% glycerin in saline, were pricked on the left forearm. In all countries, we used the same type of histamine, allergens, negative control and 1-mm tip metallic lancets (ALK-ABELLO, Hørsholm, Denmark). The lancet was pricked vertically into the skin through each drop for 2 s with firm pressure, starting with histamine 10 mg/mL. A new lancet was used for each prick test. Ten minutes after the end of the procedure, the weals were outlined with a thin felt-tip pen. The contours were transferred to the record sheet by means of translucent tape. The size of each weal was measured as the mean of the longest diameter and the diameter perpendicular to it at its mid point. In all the three countries, all tests were done by the same two well-trained operators.

To evaluate whether the time of reading influenced the weal size, in 50 children our two operators measured histamine weals twice, at 10 and 14 min after the prick test. The mean difference between measures was 0.15 ± 0.18 mm for the 10 mg/mL concentration, and 0.05 ± 0.15 mm for the 1 mg/mL concentration; the coefficients of repeatability were 0.36 and 0.30 mm. In another 50 children, the two operators did two pricks with the same histamine concentration (10 mg/mL): weal sizes measured 10 min after the procedure yielded a mean difference between measures of 0.02 ± 0.43 mm with a coefficient of repeatability of 0.87. Lower coefficients, twice the SD of the difference between duplicate measurements, indicate higher reproducibility. These control tests complied with the currently accepted 1 mm variation around the mean of repeated measurements [38, 39].

Total and specific immunoglobulin E assay

All serum samples separated from venous blood were stored immediately at $-20\,^{\circ}C$ for transport and within 5 days at $-70\,^{\circ}C$ until tested. Aliquots of all sera were tested for total IgE and for specific IgE against the most frequently positive allergens (*D. farinae*, cat hair, *A. tenuis*, mixed grasses 1, and mixed grasses 2 by the immuno-CAP method (Pharmacia, Uppsala, Sweden)). *D. pteronyssinus* was considered as a duplicate of *D. farinae* and not reported.

Statistical methods

Kolmognorov–Smirnov test was used to assess normal distribution of variables. Non-normal values were transformed into natural logarithms. Results are expressed as geometric mean (or arithmetic mean for normally distributed data) and 95% confidence intervals. Mann–Whitney *U*-test was used to compare two independent groups of non-normally distributed data. Kruskal–Wallis test was used for multiple comparisons of non-normally distributed data with *post hoc* Dunn's test to assess significant differences between pairs. One-way ANOVA with *post hoc* Scheffe test was applied for multiple comparison of normally distributed data. The χ^2 test was used to compare the frequency of reactivity to allergens and of positive specific IgE. Binary logistic regression was performed to assess the relationship between outcomes of ASPT (larger than zero but less than 3 mm, or $\geqslant 3$ mm) as dependent variable and Country, serum specific IgE and HSR as independent variables and between low or high histamine weal as dependent variable and serum specific IgE, ASPT, with or without Country, as independent variables. The statistical software, statistical package for social sciences (SPSS Inc., Chicago, IL, USA) 9.0 for Windows was used. P-values < 0.05 (by two-tailed testing) were considered to indicate statistical significance.

Results

Polish children had the lowest average HSR, Italian children had intermediate values while Libyan children had the highest values (3.75, 4.43, and 5.06 mm; $P<0.001$ by *post hoc* Scheffe's test) (Table 1). By contrast, no differences were found in total serum IgE levels in the three countries. Frequencies of detectable serum IgE antibodies (RAST $\geqslant$ 0.35 kU/L) against at least one of the allergens tested were lower in Libyan than in Italian or Polish schoolchildren (9.1%, 30.0% and 23.5%; χ^2 test between Libya–Italy and Libya–Poland, $P<0.001$). Similarly, the frequency of participants with at least one allergen-specific weal reaction with a diameter of $\geqslant$ 3 mm was significantly lower among Libyan schoolchildren than among Italian and Polish schoolchildren (4.7, 29.0, 19.6, χ^2 test between Libya–Italy and Libya–Poland, $P<0.001$). The differences in the prevalence of subjects with positive ASPTs values in the three countries changed with the different thresholds for positive allergen weals (Table 2). For example, the 2-mm cut-off yielded a 2–4 higher prevalence of atopy in Italy than in Libya; whereas 4-mm cut-offs increased this ratio to values of 5 and 20. Conversely, the ratio between Poland and Italy remained substantially unchanged regardless of the threshold. Similar differences among the three countries remained evident when we used as a criterion for positive weal dimension a weal measuring the same or larger than half the histamine weal.

The amount of serum-specific IgE found in children with an allergen weal of different dimensions differed in the three countries: for each size of ASPT children in Poland invariably had higher specific IgE values than children in Libya and Italian children always had values midway between those of the other two countries (Table 3).

When we subdivided the whole population of children with measurable ASPT (weals >0 mm in diameter) according to their HSR (higher or lower than the 50° percentiles for each country) those with higher HSR had lower serum-specific IgE. Results were significant for children with ASPT weals $\geqslant$ 3 mm in diameter, both for each country and for the whole population adjusted for countries ($P = 0.008$) suggesting that HSR strongly influenced the relationship between ASPT and serum-specific IgE. This finding was even more evident when we restrict the analysis to children with measurable ASPT for *D. farinae* ($P<0.001$) (Fig. 1).

When we performed a logistic regression with Country, serum-specific IgE and HSR as independent variables and ASPT outcomes as the dependent variable, we confirmed that HSR is a variable which significantly and independently influences allergen skin weal dimension (and positivity) with an odds ratio of 2.6 for *D. farinae* ($P = 0.0015$) and of 1.65 for all the allergens together ($P = 0.019$). To exclude an influence of the level of the specific IgE on HSR we also performed a similar logistic regression with low or high histamine weal dimension as a dependent variable: this analysis showed no influence of specific IgE level on HSR, both for the whole population and separately for each Country.

Discussion

Studying the three unselected groups of 9–10-year-old children from five towns in Libya, Italy and Poland we found that HSR differed in the three countries (Libya > Italy > Poland). The three countries differed also for the prevalence of atopy-positive ASPT and measurable serum-

Table 1. Unselected population of school children from three countries

	Poland	Italy	Libya
Number of children	102	217	274
Males (%)	43.1	47.0	48.5
Mean age (years, range)	9.57 (9.08; 10.17)	10.19 (9.08; 11.58)	9.04 (7.42; 11.42)
Histamine 10 mg/mL (mean diameter of skin weal (mm)) [95% CI]	3.75 [3.56–3.93]	4.43 [4.30–4.57]	5.06 [4.93–5.18]*
Histamine 1 mg/mL (mean diameter of skin weal (mm)) [95% CI]	2.35 [2.19–2.51]	3.08 [2.98–3.19]	3.20 [3.11–3.30]†
Total IgE (geometric mean (kU/L)) [95% CI]	64.60 [51.92–80.41]	56.36 [45.37–70.01]	48.66 [38.00–62.30]
Serum specific IgE (% of children with IgE $\geqslant$ 0.35 kU/L for at least one allergen)	23.5 [15.3–31.8]	30.0 [23.9–36.0]	9.1 [5.7–12.5]‡
ASPT – 1 (% of children with a skin weal for at least one allergen $\geqslant$ 3 mm)	19.6 [11.9–27.3]	29.0 [23.0–35.1]	4.7 [2.2–7.3]‡
ASPT – 2 (% of children with a skin weal for at least one allergen $\geqslant$ 1/2 histamine 10 mg/mL)	26.5 [17.9–35.0]	33.2 [26.9–39.4]	6.6 [4.3–8.9]‡

CI, confidence intervals; ASPT, allergen skin prick test.
**Post hoc* Scheffe's test for comparison between all countries, $P<0.001$.
†*Post hoc* Scheffe's test for comparison between Poland–Italy and Poland–Libya, $P<0.001$.
‡χ^2 test between Libya–Italy and Libya–Poland, $P<0.001$.

Table 2. Odds ratio for different definitions of atopy for each country with Italy as the reference

		Odds ratio for mean weal dimension (95% confidence intervals)			
Allergens	Country	$\geqslant$ 2 mm	$\geqslant$ 3 mm	$\geqslant$ 4 mm	$\geqslant$ 1/2 H-10*
Dermatophagoides farinae	Poland	0.72 (0.39–1.33)	0.69 (0.03–0.23)	0.71 (0.32–1.58)	0.96 (0.53–1.73)
	Libya	0.25 (0.14–0.45)	0.09 (0.03–0.23)	0.02 (0.01–0.20)	0.13 (0.06–0.28)
At least one allergen positive	Poland	0.59 (0.35–1.02)	0.60 (0.34–1.05)	0.53 (0.27–1.03)	0.72 (0.43–1.22)
	Libya	0.33 (0.21–0,51)	0.12 (0.06–0.23)	0.08 (0.03–0.19)	0.14 (0.08–0.25)

*Allergen weal $\geqslant$ half the dimension of the weal elicited by histamine 10 mg/mL.

Table 3. Geometric mean of the specific IgE (95% confidence intervals) corresponding to each allergen weal size

Country	No. of tests	>0–<2 mm	No. of tests	2–<3 mm	No. of tests	⩾3 mm
Poland	14	0.14 (0.09–0.17)	14	0.80 (0.34–1.86)	31	11.51† (6.64–19.96)
Italy	18	0.14 (0.11–0.19)	50	0.42 (0.29–0.60)	121	3.47 (0.92–5.12)
Libya	36	0.15 (0.10–0.22)	45	0.22* (0.14–0.33)	22	1.25 (0.44–3.54)

*$P<0.05$ for comparison Poland–Libya and Italy–Libya by *post hoc* Dunn test.
†$P<0.05$ for comparison Poland–Libya and $P<0.01$ for Poland–Italy by *post hoc* Dunn test.

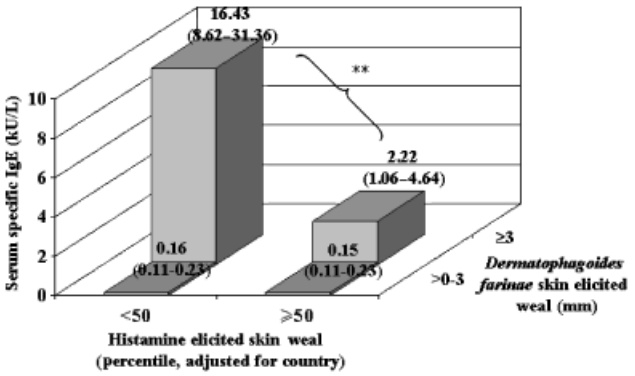

Fig. 1. Serum specific IgE for *Dermatophagoides farinae* in subjects with measurable skin weal elicited by this allergen and with higher or lower histamine skin reactivity. Values are reported as geometric means with 95% confidence interval. In children with allergen elicited weals ⩾3 mm serum-specific IgE were significantly higher in those with low skin reactivity ($P = 0.001$ by Mann–Whitney *U*-test).

specific IgE (Italy although higher, not significantly higher than Poland, and both these countries substantially higher than Libya). In answer to our basic question, differences in HSR strongly influenced the relationship between positive ASPT and RAST: children with low HSR needed more than twice the amount of serum-specific IgE to build up an allergen skin weal of 3 mm or more. From a biological perspective, our data reinforce the concept that allergen skin reactions involve at least two different and independent mechanisms [30], i.e. the specific interaction between allergen and IgE antibodies bound to mast cell membranes and the subsequent tissue response to histamine released from mast cells themselves. Our current findings [31, 32, 36] therefore imply that HSR can no longer be considered a fixed, personal character interfering with the 'true' prediction of allergen responsiveness (atopy) [3, 5]. On the contrary, it should be considered a variable that in conjunction with, but independently from atopic mechanisms, determines the body response to allergen exposure. Our findings suggest that the same amount of histamine released as a consequence of the IgE-allergen interaction is more 'efficient' in inducing skin weals in those populations (or individuals) with higher HSR.

Over the past decades, many studies have underlined the need to 'correct' allergen-elicited weals for HSR [3, 18, 20]. Our findings in this study, vice-versa, suggest that from a clinical viewpoint, allergen weal diameters should no longer be adjusted for individual HSR. If reactivity to allergens arises from two coexisting but independent components, measuring only one of them (atopy) by adjusting for the other (non-specific skin reactivity to histamine) reduces the information given by the SPT procedure. The clinical meaning of a prick test, i.e. the ability to predict the symptoms elicited by any future allergen exposure, is probably better expressed by the weal dimensions themselves than by their simple 'atopic' component. We strongly support the concept that 'skin hyper-responsiveness' to histamine may be as relevant in the study of allergic diseases as 'bronchial hyper-responsiveness' to histamine and methacholine is relevant in the study of asthma.

HSR should therefore be considered as an independent variable to be evaluated in epidemiological studies on allergy. A point of discussion is the reproducibility of this variable in epidemiology [39], in this study when we explicitly checked HSR, we found good repeatability. International epidemiological studies on atopic diseases in the various countries (e.g. ISAAC) may need to consider that a given response to ASPTs should be interpreted differently according to the aspecific component of the weal reaction to allergens, HSR. Expressing ASPT responses as a graduated scale based on the allergen–histamine weal ratio [18, 20, 25] may be appropriate only in studies examining subjects living in the same study area, whereas it undoubtedly distorts the results of international studies comparing countries with different life-styles. Thus the amount of serum-specific IgE is difficult to predict if the same cut-off point of a weal diameter is used in countries with different life-styles. Also the maximal diagnostic efficiency of ASPT [40], beyond the scope of this epidemiological survey, should probably be assessed separately in each different population.

Like the atopic predisposition to produce IgE, HSR is probably under genetic control [29]. Yet considering that HSR can significantly differ among countries but can also significantly increase over time [31] it presumably also strongly reflects the influence of various as yet unknown environmental factors.

In this paper, we challenge the concept that the observed time-related increase or differences in HSR mainly or solely arise from westernization. Our results suggest otherwise. Children living in the deep African continent, albeit isolated at the border of the Sahara desert, hypothetically far from western life-style, had twofold higher HSR than the children from the European countries. Hence, we believe that the HSR differences found in the populations reported here reflect a complex, dynamic, environmental interaction that should be monitored in the different parts of the world.

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