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Disagreement between Skin Prick Tests and Specific IgE in Early Childhood

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Key Words
Agreement · Atopic dermatitis · Childhood · Sensitization · Skin prick test · Specific IgE

Abstract
Background: Accurate diagnosis of allergic sensitization is essential in clinical practice and allergy research, and the choice of assessment method may have an important impact. The PASTURE study (Protection against Allergy: Study of Rural Environment) examines the influence of exposure to a dairy farm environment on the occurrence of allergy in a cohort of rural European children from birth to 10 years. The aim of our study was to analyze agreement between skin prick tests (SPTs), to aeroallergens and food allergens, and specific IgE and to evaluate the association of SPT with atopic dermatitis in the 204 French children of the PASTURE study. ***Methods:*** SPT, atopic dermatitis assessment, and specific IgE measurements were performed at 1, 4.5, and 6 years. ***Results:*** A total of 137 children attended all three visits. The agreement between SPTs and specific IgE was poor except for perennial aeroallergens at 6 years and for an IgE cutoff greater than 0.7 IU/ml (κ = 0.69, 0.5202 – 0.8621). The prevalence of positive SPTs increased with age. Positive SPTs were transient at 1 year, whereas they were persistent between 4.5 and 6 years. Positive SPTs at 1 year were predictive of the occurrence of atopic dermatitis during follow-up. ***Conclusion:*** SPTs did not have good agreement with serum-specific IgE in early childhood. Both tests (SPT and specific IgE) should be used. Skin allergenic reactivity increased with age and was transient at 1 year but associated with the occurrence of atopic dermatitis.

Introduction

Although the prevalence of allergic diseases is increasing, it is important to note that common allergic-type symptoms are not always due to atopy. Therefore, an accurate diagnosis of the presence of allergy is an important public health issue [1], especially in early childhood.

In pediatric practice as in allergy research, measurement of the serum-specific IgE (SSIgE) level is generally preferred over the skin prick tests (SPT) for reasons relating to time, training in performing SPT, availability of allergen extracts, and (in some countries) safety reasons. In most studies on the occurrence of atopic dermatitis (AD) in childhood, sensitization against most common allergens is assessed by SSIgE [2].

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However, it remains unclear whether SSIgE and SPT can be used interchangeably. Very few studies have compared SPT and SSIgE head-to-head, prospectively and over time, either in the general population [3] or in early childhood [4, 5].

The PASTURE study (Protection against Allergy: Study of Rural Environment) birth cohort was established to confirm the protective effect of a farming environment that was observed in previous cross-sectional studies on the development of childhood atopy and to analyze the mechanisms of protection [6]. To date, this cohort has included 1,133 families in rural areas of 5 European countries (Austria, Finland, France, Germany, and Switzerland). SSIgE assays were performed in the whole cohort, whereas SPTs were performed only in the French arm. This offers a unique opportunity to determine how early allergenic sensitization in rural children was assessed by SPTs and SSIgE.

The aims of our study, which focused on children living in a rural environment, was to analyze (1) the agreement between SPTs and SSIgE and (2) the course of SPT results from 1 to 6 years and the relationship between allergic sensitization and the occurrence of AD.

Materials and Methods

Design and Study Population

The design of the PASTURE study has previously been described in detail elsewhere [6]. The French arm of the cohort included 204 families at the third term of the mother's pregnancy in 2003. They were classed into two groups: the farmer group, comprising 95 children whose parents lived on a dairy farm and the nonfarmer group, comprising 109 children whose parents lived in the same rural areas but did not live on a farm. The inclusion and exclusion criteria were those of the overall PASTURE study [7]. Additional exclusion criteria specific to SPT were added, namely, we excluded patients with immunosuppressive or steroid therapy during the previous 2 months, antihistamine treatment within the last 7 days, and diffuse skin lesions. Data were considered noninterpretable when the 'positive' control SPT (histamine) was negative. The study was approved by the French research ethics committee (CPP), and written informed consent was obtained from all parents.

The children were seen when they were 1, 4.5, and 6 years old. SPT and SCORAD evaluation [8] were performed at each visit. Blood sampling for SSIgE measurement was performed at each visit. SPT and SSIgE measurements were performed at all three visits for 137 and 139 children, respectively. Parental history of allergy was defined as at least one parent ever having asthma, hay fever, or AD; this information was self-reported.

Atopic Dermatitis

AD was evaluated at each visit by the SCORAD index. We defined 'SCORAD AD' as a positive SCORAD score (>0), and 'doctor's AD' as AD diagnosed by a doctor and reported by the parents in the questionnaires between 1 and 6 years of age. The 'cumulative prevalence of AD' was defined as a SCORAD AD at least at one visit and/or a doctor's AD at least once [9].

Skin Prick Tests

SPTs were performed on the anterior part of the forearm using a Stallerpoint® (Stallergenes, Antony, France). The test solution was applied as a drop with the use of a vial. Vertical pressure was applied with the Stallerpoint® followed by a 90-degree clock-wise rotation. We used allergen extract solutions Alyostal Prick® (Stallergenes) for 13 aeroallergens (house dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, cat, dog, *Dactylis glomerata*, birch pollen, grass pollen, alternaria, hazel pollen, olea, cereals, mugwort, and plantain) and 5 food allergens (hen's egg yolk, hen's egg white, cow's milk, peanut, and soybean). Reading was performed 15–20 min later by a pediatric allergist. Positive SPT was defined as a wheal diameter ≥3 mm above the negative control.

SSIgE Measurements

Blood sampling was performed according to Standard Operating Procedures of the PASTURE study. We applied a topical anesthetic EMLA® plaster (AstraZeneca, Wedel, Germany) 60 min before the blood sampling. Blood sampling was performed under sterile conditions and with the use of a venous puncture set.

SSIgE measurements were performed using the Allergy Screen Test Panel (Mediwiss Analytic, Moers, Germany). Details of this assay and its validation have previously been published [10]. Tests were performed for 13 aeroallergens (house dust mites *D. pteronyssinus* and *D. farinae*, cat, dog, horse, ryegrass, grass pollen, alternaria, hazel pollen, mugwort, plantain, birch pollen, and alder pollen) and 6 food allergens (hen's egg, cow's milk, hazelnut, carrot, peanut, and wheat flour).

We defined the prevalence of positive SPTs as the number of children with at least one positive SPT, and the prevalence of positive SSIgE as the number of children with at least one positive SSIgE, at any given time point.

Statistical Analysis

To analyze agreement between SPT and SSIgE, we used Cohen's kappa coefficient (κ). Several cutoffs for the definition of 'positive SSIgE' were studied, namely 0.2, 0.35, 0.7, and 3.5 IU/ml. To analyze the association between positive SPTs at 1 year and positive SPTs at later time points, we used McNemar's test (Epi Info software, version 3.3.2, Atlanta, Ga., USA). To analyze the relationship between allergic sensitization and AD, we used the χ^2 test or Fisher's exact test, as appropriate, and we calculated the diagnostic values of SPTs for the cumulative prevalence of AD.

Results

Relationship between SPT and SSIgE

The prevalence of positive SPTs increased with age (9.5% at 1 year, 14.2% at 4.5 years, and 22.5% at 6 years; fig. 1a). Sensitization to food allergens decreased with age, whereas sensitization to seasonal and perennial increased

with age. The prevalence of positive SPTs was lower in the farmer group than in the nonfarmer group at all three visits (8.5 vs. 10.4% at 1 year, 9.6 vs. 19.4% at 4.5 years, and 18.5 vs. 26.9% at 6 years) and for all categories of allergens, but this difference was significant only at 4.5 years for seasonal aeroallergens ($p < 0.05$).

The prevalence of positive SSIgE (>0.35 IU/ml) was 41% at 1 year, 48.2% at 4.5 years, and 40.3% at 6 years (fig. 1b). Positive SSIgE to perennial aeroallergens decreased with age, whereas SSIgE to food and seasonal aeroallergens increased between 1 year and 4.5 years. There was no difference between the farmer and nonfarmer groups, regardless of the chosen cutoff. Positive SPTs and positive SSIgE (>0.35 IU/ml) by category of allergens at each visit are presented in table 1 with p values showing the difference between the two methods.

The profile of allergenic sensitization, detected by SSIgE or SPT, was different, even using higher cutoffs to define positive SSIgE. Agreement between both tests was globally weak, with a poor κ-coefficient. Agreement increased with age and with higher cutoff levels for SSIgE (table 2).

Course of SPT Results from 1 to 6 Years

We observed 4 profiles of sensitization, namely persistent (positive or negative at all three visits), transient (negative at 6 years and positive earlier), incident (negative at 1 year and positive later), and intermittent (positive at least once and negative at least once).

SPTs were positive at least once during the follow-up for 30.7% of the children. Among the children with positive SPT, 7.1% had persistent, 61.9% incident, 14.3% transient, and 16.7% intermittent sensitization. Transient sensitization was only observed at 1 year and represented 75% of children with positive SPTs at 1 year. Among the children with positive SPTs at 4.5 years, 79% had persistent SPTs at 6 years. Parental history of allergy was noted for 37.5% of children with positive SPTs at 1 year versus 22.4% of children with negative SPTs at 1 year ($p = 0.45$).

Relationship between Allergic Sensitization and Occurrence of AD

SCORAD AD decreased with age. There was no difference between the farmer and nonfarmer groups at 1 or 4.5 years, whereas there was a nonsignificant difference ($p = 0.18$) between groups at 6 years (fig. 1c). The cumulative prevalence of AD was 46.9%, and there was no difference between groups.

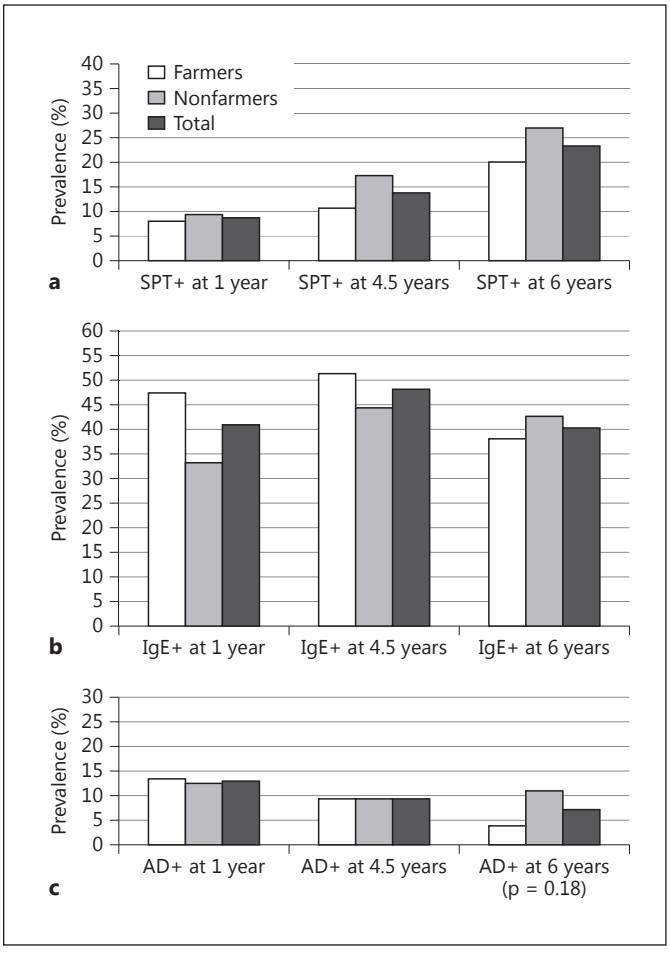

Fig. 1. Prevalence (%) of positive SPTs (**a**), positive serum-specific IgE >0.35 IU/ml (**b**) to at least one allergen, and SCORAD-defined AD (**c**) at each visit depending on the child's status (born and living on a farm or in a nonfarming family).

There was no significant relationship between positive SPT and SCORAD AD at each time point. However, there was a significant correlation between positive SPT at 1 year and the presence and/or occurrence of AD during the 6 years of follow-up (specificity 96%, positive predictive value 78.6%, $p = 0.007$). Among the children who had positive SPT at 1 year and AD at least once during the 6-year follow-up, 91.6% were sensitized to food allergens (83% to egg).

In contrast, there was no significant relationship between positive SSIgE at 1 year and the presence and/or occurrence of AD ($p = 0.12$). The relationship was positive only when we focused on positive SSIgE to food allergens ($p = 0.03$).

Table 1. Number of positive SPTs and positive SSIgE (>0.35 IU/ml) by category of allergen at each visit

		1 year			4.5 years			6 years		
		SSIgE+	SSIgE–	p	SSIgE+	SSIgE–	p	SSIgE+	SSIgE–	p
Seasonal aeroallergens	SPT+	0	0	0.0412	11	3	0.0005	16	5	0.1456
	SPT–	6	154		21	117		12	123	
Perennial aeroallergens	SPT+	1	2	<0.0001	5	4	0.0139	15	6	0.1686
	SPT–	56	101		16	128		13	122	
Food allergens	SPT+	2	11	0.2652	0	1	<0.0001	2	3	<0.0001
	SPT–	18	129		52	99		31	120	
Any allergens	SPT+	10	6	<0.0001	19	3	<0.0001	28	8	0.0001
	SPT–	61	83		54	76		34	86	

p values obtained with McNemar's χ^2 test.

Table 2. Values of the κ-coefficient to assess agreement between allergenic sensitization as evaluated by SPT and by SSIgE according to age at the study visit and to the IgE cutoff value

		IgE >0.2 IU/ml		IgE >0.35 IU/ml		IgE >0.7 IU/ml		IgE >3.5 IU/ml	
		κ	95% CI	κ	95% CI	κ	95% CI	κ	95% CI
1 year	Any allergen	0.07	–0.020; 0.163	0.08	–0.022; 0.189	0.07	–0,059; 0.211	0.21	–0,027; 0.453
	Food allergens	0.03	–0.124; 0.184	0.02	–0.141; 0.187	0.03	–0.143; 0.201	0.12	–0.096; 0.343
	Perennial aeroallergens	0.05	–0.005; 0.109	–0.001	–0.058; 0.056	–0.03	–0.076; 0.003	–0.02	–0.046; –0.005
	Seasonal aeroallergens	0.16	–0.115; 0.429	0.28	–0.153; 0.709	–	–	–	–
4.5 years	Any allergen	0.17	0.081; 0.263	0.23	0.114; 0.342	0.34	0.187; 0.491	0.37	0.157; 0.578
	Food allergens	–0.13	–0.039; 0.012	–0.01	–0.038; 0.012	–0.01	–0.037; 0.012	–0.01	–0.027; 0.006
	Perennial aeroallergens	0.17	0.001; 0.347	0.27	0.051; 0.495	0.29	0.037; 0.558	0.44	0.135; 0.744
	Seasonal aeroallergens	0.34	0.171; 0.516	0.40	0.216; 0.587	0.54	0.326; 0.750	0.34	0.070; 0.611
6 years	Any allergen	0.29	0.163; 0.429	0.39	0.252; 0.537	0.57	0.427; 0.717	0.59	0.433; 0.749
	Food allergens	0.03	–0.069; 0.136	0.05	–0.071; 0.176	0.04	–0.122; 0.209	–0.02	–0.044; –0.005
	Perennial aeroallergens	0.43	0.266; 0.602	0.54	0.361; 0.722	0.69*	0.520; 0.862	0.39	0.174; 0.625
	Seasonal aeroallergens	0.53	0.352; 0.701	0.59	0.416; 0.764	0.66*	0.493; 0.832	0.69*	0.507; 0.868

* κ >0.61, indicating good agreement.

Discussion

Our study in a cohort of rural children shows that the relationship between SPT and SSIgE was very weak but increased with age and higher cutoffs, suggesting that these two tests cannot be used interchangeably to assess IgE-related allergic sensitization in early childhood. While SPT sensitization increased with age, AD prevalence decreased. The cumulative prevalence of AD was significantly correlated with positive SPTs at 1 year, mostly reacting to food allergens.

The comparison of both tests at three different time points in a general population of preschool children is original. The nonselected nature of the PASTURE population is unique and allows generalization of the findings. In our study, there were significantly more children with positive SSIgE than children with positive SPTs at all visits. The choice of the method for each test may have had some consequence.

Regarding the method chosen for SPT, the Stallerpoint® device was found to be less sensitive than the ALK lancet or IV needle by Masse et al. [11]. Nevertheless, the 90-degree clock-wise rotation was found to improve the sensitivity of this technique. By contrast, this technique was described by Buyuktiryaki et al. [12] as reliable, tolerable, and comparable with the ALK lancet technique.

Regarding the method chosen for SSIgE, Wood et al. [13] showed some differences in SSIgE results according to the method of assay. However, Herzum et al. [10] found that the Allergy Screen panel yields reliable results in the detection of allergic sensitization to common allergens.

However, the higher sensitivity of SSIgE detection, previously reported in a prospective 18-month study [14], does not alone explain why the agreement between both tests was so poor in our study. The strength of agreement was only substantial [15] for aeroallergens at 6 years of age and for cutoffs of 0.7 and 3.5 IU/ml. The recent meta-analysis by Soares-Weiser et al. [16] reported that very few studies have compared the tests head-to-head in the same population over time. In their populations of food-allergic subjects without age limits, SPT and SSIgE were both sensitive but not specific. In the DARC birth cohort, Kjaer et al. [17] showed that SPTs were better correlated with a diagnosis of allergic disease at 6 years than SSIgE. In a recent article on the $COPSAC_{2000}$ at-risk birth cohort, Schoos et al. [5] also found a substantial disagreement between SPT and SSIgE in early childhood with all κ-coefficient under 0.60 without increasing with age.

The marked difference between the results obtained using SPT and those obtained with SSIgE is probably due to many factors. Each test can be performed by different methods [13] and influenced by various factors [18]. It has been suggested that SPT and SSIgE may be associated with specific and different atopic diseases [19], probably even more so in early life. Based on our results and on the pathophysiology of the IgE-dependent immune reactions, we fully agree with the conclusions of a Norwegian study [20] that compared SSIgE measurement and SPTs in 353 two-year old children. In this study, both tests yielded different results, were not similar in the detection of atopic sensitization, and actually reflected distinct aspects of the IgE-related immune response. Schoos et al. [5] also suggested as an explanation for the disagreement between both tests that the immune response is different in the skin and in the blood. In the review article by de Vos [21], most studies showed substantial discordance between SSIgE and skin-testing results, suggesting that the two testing methods complement each other. These authors concluded that if only one type of testing is performed, a substantial number of allergic sensitizations may be missed.

The progressive increase in the agreement between both tests in line with age is consistent with the transient and poorly explained nature of allergic sensitization to food allergens in very early childhood. However, SPTs at 1 year, which are more related to food sensitization, are definitely associated with AD in the 6 first years of life, whereas SSIgE levels are not. The concomitant increase in agreement when higher cutoffs are used for SSIgE results also raises some doubts about the biological relevance of low SSIgE levels. It would also have been interesting to study various cutoffs for SPT positivity, but in our study very few children had SPT >4 mm, thus precluding further analysis. However, Bousquet et al. [3] showed that there was no increase in agreement between both tests with higher SPT cutoff levels.

Our study made it possible to describe the course of allergic sensitization in early childhood, as evaluated by both SPT and SSIgE in a nonselected rural population. Increased atopic sensitization with age has previously been described, but mostly in populations with risk factors for atopy [5, 22, 23] or with atopic diseases [24], and in school-age children [25]. Few studies have addressed SPT sensitization in populations of children not selected for their predisposition to atopy. The transient nature of SPTs at 1 year has already been suggested in the Isle of Wight cohort [26], in which 80% of positive SPTs were transient at 1 year. In addition, our 6-year follow-up showed that SPTs became persistent between 4.5 and 6 years, with almost 80% persistent SPTs. This could reflect environmental exposure but also maturation of the immune system, with an age-dependent increase in capacity either to respond to or to tolerate various types of allergens. The prevalence of positive SPTs by category of allergens changed during early childhood, with food sensitization predominant at 1 year and decreasing thereafter, whereas aeroallergen sensitization was low at 1 year and subsequently increased. Similar findings were observed by Rhodes et al. [23] in a birth cohort with family atopy.

Our study suggests that SPT sensitization at 1 year, albeit transient, is associated with the presence and occurrence of AD. Most positive SPTs at 1 year in children who had AD during follow-up were directed against food allergens, especially egg allergens, as previously reported by van Asperen et al. [27]. The role of sensitization to food allergens in AD has been suggested by several studies in children with AD [28, 29], and the course of AD has been reported to be significantly related to the presence of SSIgE to egg [30]. Few studies have focused on the prediction of AD by early sensitization to food allergens, as assessed by SSIgE, and even less so by SPT. In the DARC birth cohort [17], the early presence of food SSIgE was a highly significant predictor of allergic diseases at 6 years, especially for AD, whereas children sensitized early to in-

halant allergens had no increased risk of allergic disease at 6 years. The overall evaluation of SSIgE in the entire PASTURE cohort at 1 year showed an interesting correlation with maternal atopy [31], which might thus be the real cause of the link between food-related IgE antibodies and AD. However, in our subgroup from the PASTURE study, the extremely poor agreement between AD and SSIgE detected at 1 year and the absence of a statistically significant correlation between parental history of allergy and positive SPT at 1 year render this hypothesis highly unlikely. Although the pathophysiological meaning of the predictive value of early sensitization to egg allergens for AD occurrence remains obscure, this finding could be used to select at-risk children for closer follow-up in order to detect any further development of atopic diseases and/or for interventional studies in the future.

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