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Skin prick test and specific serum IgE in the diagnostic evaluation of suspected cow's milk and hen's egg allergy in children: does one replace the other?

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Abstract

Background The measurement of specific serum immunoglobulin E (sIgE) and the skin prick test (SPT) are accepted tools in the diagnostic work-up of suspected food allergy. Often only one of the methods is used to determine sensitization; however, it is still under debate whether these two methods can be used interchangeably.

Objectives To investigate the concordance of SPT and sIgE serum assays with regard to suspected food allergy.

Methods In 395 children referred to our clinic with suspected cow's milk allergy and in 268 children with suspected hen's egg allergy specific immunoglobulin E (IgE) was measured, a SPT and an oral food challenge performed. A weal size ≥ 3 mm and sIgE ≥ 0.35 kU/L were considered positive. The weal size of the SPT and the level of food-specific IgE were tested for correlation for each allergen.

Results Of the 395 (23%) children orally challenged with cow's milk, 92 showed no corresponding results for SPT and sIgE as either positive or negative. For hen's egg, in 27 of 268 (10%) children differing test results for SPT and sIgE in serum were obtained. Moreover, regarding the quantitative values for sIgE and SPT in children with or without clinically relevant food allergy, sIgE and SPT correlated badly.

Conclusions The concordance between SPT and sIgE is surprisingly low for cow's milk and hen's egg on an individual basis. Therefore, the tests should not be used interchangeably. Especially in children who receive a negative test result the alternative test should also be used. Furthermore, our data indicate again that oral food challenges are still the method of choice to diagnose food allergies.

Keywords children, food allergy, immunoglobulin E, skin prick test

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Introduction

Food allergy still seems to be a rising problem in western countries [1, 2]. It is often suspected in infants and children, especially in those with pre-existing atopic dermatitis (AD) and/or a positive family history of atopic diseases [3]. This may explain the increased demand for a reliable evaluation of patients with suspected food-related symptoms, who may otherwise be unjustifiably subjected to harmful dietary restrictions [4]. The foods most commonly involved are cow's milk, hen's egg, peanut, tree nuts, soy, fish and wheat [5, 6].

Clinical reactions to foods range from mild skin symptoms to life-threatening anaphylactic reactions [7–10].

Controlled oral food challenges still represent the “gold standard” for diagnosing food allergy [6, 10–16]. However, they are time-consuming, troublesome for the patients and not without risk of even severe allergic symptoms. Therefore, there is a need for instruments that may make controlled oral food challenges superfluous—at least in part. In particular, a negative result should exclude clinically relevant reactions.

The majority of food allergies in children are mediated by immunoglobulin E (IgE). Therefore, one of the

first steps in the diagnostic work-up of children with suspected food allergy is the determination of the presence of IgE antibody to specific foods using skin prick test (SPT) or serum assays. Both techniques are widely accepted diagnostic tools [17–25]. However, they merely detect sensitization and do not necessarily indicate clinical relevance. Hence, several authors have shown a correlation between the level of sIgE and the likelihood of clinical reaction and established so-called “decision points”, which predict clinically relevant food allergy [26–32]. However, the findings vary considerably between authors and seem to be dependent on the allergen and the population studied [33, 34]. SPTs have been used for decades to prove or exclude sensitization to allergens. As with sIgE, several studies proposed “cut-off” values of weal sizes [20, 30, 35–40]. However, taken together, the results of the SPT also vary considerably in the literature and are only provided for some foods.

Despite these limitations, international position papers and guidelines commonly propose the performance of only one of the tests if food allergy is suspected; either appears appropriate if no contraindications exist such as urticaria factitia in SPT [17, 41, 42]. As both are IgE-dependent test instruments, one could assume that comparable test results should be obtained in the same patient, so they might be used interchangeably. However, as yet, no study has examined the concordance of SPT and sIgE results and whether the performance of sIgE or performance of SPT should be preferred in the diagnostic work-up of suspected food-related symptoms.

This study draws on data from a large number of children to examine the concordance of SPT- and sIgE-results for cow's milk and hen's egg and to compare these tools in relation to the outcome of oral food challenges.

Methods

Study population

We studied retrospectively 501 children referred consecutively to our department for evaluation of suspected food allergy: 395 for cow's milk allergy and 268 children with suspected hen's egg allergy. Suspicion was defined as either the feeling of the parents that cow's milk or hen's egg could contribute to clinical symptoms of the child (e.g. angioedema after food intake) or that sIgE was elevated or SPT test positive in a child with eczema and the food had not been introduced into the child's diet so far. Children with a history of anaphylaxis within the last 12 months to a clearly identified causative allergen and the detection of sensitization did not undergo

oral food challenge test. Only children undergoing all the three tests required for this study (oral food challenge, determination of sIgE and SPT) were included in the study.

Skin Prick Test

Skin prick tests were performed prior to the oral food challenge. For SPTs, native foods were used: one drop of each fresh cow's milk containing 3.5% fat or native hen's egg (whisked white of egg and yolk). SPTs were performed with 1 mm single-peak lancets (ALK, Copenhagen, Denmark). We used 10 mg/mL histamine dihydrochloride (ALK) as a positive control and saline solution as a negative control. SPTs were read after 15 min. All tests with a weal diameter below 3 mm elicited by histamine or with a weal of ≥ 2 mm by the negative control were excluded. SPT was assessed as positive if the weal diameter was ≥ 3 mm [43].

Specific serum IgE

Blood was drawn directly prior to the oral food challenge. Patient sera were analysed for concentrations of specific IgE antibody titres to cow's milk and hen's egg, determined by FEIA using the ImmunoCAP® (Phadia, Uppsala, Sweden) [44]. Children were regarded as sensitized if specific IgE was ≥ 0.35 kU/L.

Oral food challenges

Oral food challenges were performed as a result of a suggestive medical history, and/or positive SPT, and/or elevated sIgE level. We analysed the two most common IgE-mediated food allergens in European children: cow's milk and hen's egg. A total of 289 of the 395 challenges with cow's milk (73%) and 186 of the 268 challenges with hen's egg (69%) were performed as double-blind, placebo-controlled food challenges (DBPCFC). Open challenges were allowed in younger children who had a clear history of immediate type reactions. The clinical dietician randomized and prepared the challenges. Briefly, successive doses (0.1, 0.3, 1.0, 3.0, 10.0, 30.0 and 100.0 mL corresponding to 3 mg–3.3 g protein) of fresh pasteurized cow's milk containing 3.5% fat or placebo (Neocate, SHS, Liverpool, UK) were administered at least 30 min apart [14, 45, 46]. For hen's egg, pasteurized hen's egg (white and yolk) was administered in a similar way using semilog increases ranging from 5 mg to 4.6 g protein. Oral food challenges were performed and evaluated in detail as described previously and regarded as positive if objective symptoms were observed [27, 34, 47].

Statistics

For the statistical analysis, we used SPSS for Windows (version 17.0). Spearman rank correlation test was used and comparisons were considered significant for $P < 0.05$.

Ethics Statement

The study was approved by the institutional ethics committee.

Results

Study population and clinical outcome of food challenge

We studied a total of 663 oral food challenges in 501 children: 395 with cow's milk and 268 with hen's egg (Table 1). For cow's milk, patients' age ranged from 3 months to 13 years (median 12 months) and for hen's egg from 4 months to 14 years (median 16 months).

A total of 209 children challenged with cow's milk had a history of a suspected allergic reaction and 62 had no previous reaction reported. In hen's egg, 49 children had a history of a possible reaction and 71 had no reaction reported. Of these 71 children, 11 had never had hen's egg introduced into their diet. Information about previous reactions was missing or inconclusive for 124 patients challenged with cow's milk and 148 children undergoing hen's egg challenge.

Fifty-two percent of cow's milk challenges and 73% of hen's egg challenges were assessed as positive

(Table 1). A total of 64 of 162 children who underwent evaluation for both cow's milk and hen's egg had positive reactions to both allergens.

Outcome of SPT

A total of 395 SPTs were performed with cow's milk and 268 with hen's egg. For *cow's milk*, 57% of the SPTs were assessed as positive. The median weal diameter of SPTs was 4.5 mm with a range 0–20 mm. For *hen's egg*, 82% of SPTs were assessed as positive, with a median weal diameter of 8.0 mm (range 0–25 mm).

For *cow's milk*, 14% of the patients had a positive SPT, but no clinical reaction upon challenge (Table 1). On the other hand, 8% of the patients had a negative SPT for cow's milk, but the oral provocation was positive (Table 1). Similar results were obtained for *hen's egg*. Results are shown in Table 1.

Outcome of specific serum IgE

A total of 395 measurements of food-specific IgE were performed for cow's milk and 268 for hen's egg. For *cow's milk*, sIgE ranged from 0 to 796 kU/L (median 1.3 kU/L). Based on a detection level of ≥ 0.35 kU/L 276, children (70%) were sensitized to cow's milk. For *hen's egg*, sIgE ranged from 0 to 366 kU/L (median 4.0 kU/L) and 230 (86%) were considered to be sensitized. Table 1 shows sIgE results in combination with the results of food challenge and SPT.

Table 1. Absolute numbers and (percentages) for positive and negative oral food challenges (OFC), skin prick tests (SPT) and allergen-specific IgEs (sIgE). Specific IgE ≥ 0.35 kU/L and SPT weal size diameter ≥ 3 mm were considered positive are shown. Highlighted in grey and bold are the inconsistencies between positive and negative results for SPT and specific IgE

		Cow's milk ($n = 395$)						Hen's egg ($n = 268$)					
		OFC		SPT		sIgE		OFC		SPT		sIgE	
		pos	neg	pos	neg	pos	neg	pos	neg	pos	neg	pos	neg
OFC	pos	205 (52%)*	-	172 (84%)	33 (16%)	179 (87%)	26 (13%)	195 (73%)*	-	182 (93%)	13 (7%)	187 (96%)	8 (4%)
	neg	-	190 (48%)*	54 (28%)	136 (72%)	97 (51%)	93 (49%)	-	73 (27%)*	39 (53%)	34 (47%)	43 (59%)	30 (41%)
SPT	pos			226 (57%)*	-	205 (52%)*	21 (5%)*			221 (82%)*	-	212 (79%)*	9 (3%)*
	neg			-	169 (43%)*	71 (18%)*	98 (25%)*			-	47 (18%)*	18 (7%)*	29 (11%)*
sIgE	pos					276 (70%)*	-					230 (86%)*	-
	neg					-	119 (30%)*					-	38 (14%)*

*Percentages are based on the total number of patients challenged with the according allergen ($n = 395$ for cow's milk and 268 for hen's egg). If not indicated, percentages are based on the number of patients with a positive (and negative respectively) OFC result to the according allergen.

Table 2. Shown are the absolute numbers and (percentages) for different combinations of positive and negative specific IgE and SPT in regard to the outcome of the oral food challenge test

	Total	Positive challenge	Negative challenge
<i>Cow's milk</i> (<i>n</i> = 395)			
Specific IgE positive and SPT-positive	205 (52%)	161 (41%)	44 (11%)
Specific IgE positive and SPT-negative	71 (18%)	18 (5%)	53 (13%)
Specific IgE negative and SPT-positive	21 (5%)	11 (3%)	10 (3%)
Specific IgE negative and SPT-negative	98 (25%)	15 (4%)	83 (20%)
<i>Hen's egg</i> (<i>n</i> = 268)			
Specific IgE positive and SPT-positive	212 (79%)	178 (66%)	34 (13%)
Specific IgE positive and SPT-negative	18 (7%)	9 (3%)	9 (3%)
Specific IgE negative and SPT-positive	9 (3%)	4 (1%)	5 (2%)
Specific IgE negative and SPT-negative	29 (11%)	4 (1%)	25 (9%)

Comparison of SPT and sIgE

For children orally challenged with *cow's milk*, 92 of 395 (23%) showed no corresponding results for SPT

and sIgE as either positive or negative (Table 1). For *hen's egg*, in 27 of 268 (10%) children, differing test results for SPT and sIgE in serum were obtained (Table 1). In Fig. 1, we compared sIgE levels (in kU/L) with the mean size weal diameter of SPT (in mm) for both allergens in children with clinically relevant food allergy and in those without. It is clearly seen that the correlation between the levels of allergen-sIgE and the SPT with the same allergen is poor in both groups. Correlation between sIgE and SPT for children < 3 years, 3–6 years and > 6 years of age improved with rising age: for *cow's milk*, correlation coefficient was $r = 0.55$, 0.54 and 0.72 , respectively; and for *hen's egg* $r = 0.31$, 0.60 and 0.61 respectively.

There was no significant difference neither in the proportion of children with non-corresponding results for SPT and sIgE nor the correlation coefficient r in children undergoing DBPCFC and those who had open food challenge (data not shown).

Discussion

Several factors influence the choice between the two IgE test systems, SPT and sIgE. Among these lower costs and immediate availability of the test results are in favour of the SPT, whereas independence of drug use (antihistamine or topical steroid) and skin condition favour sIgE measurement.

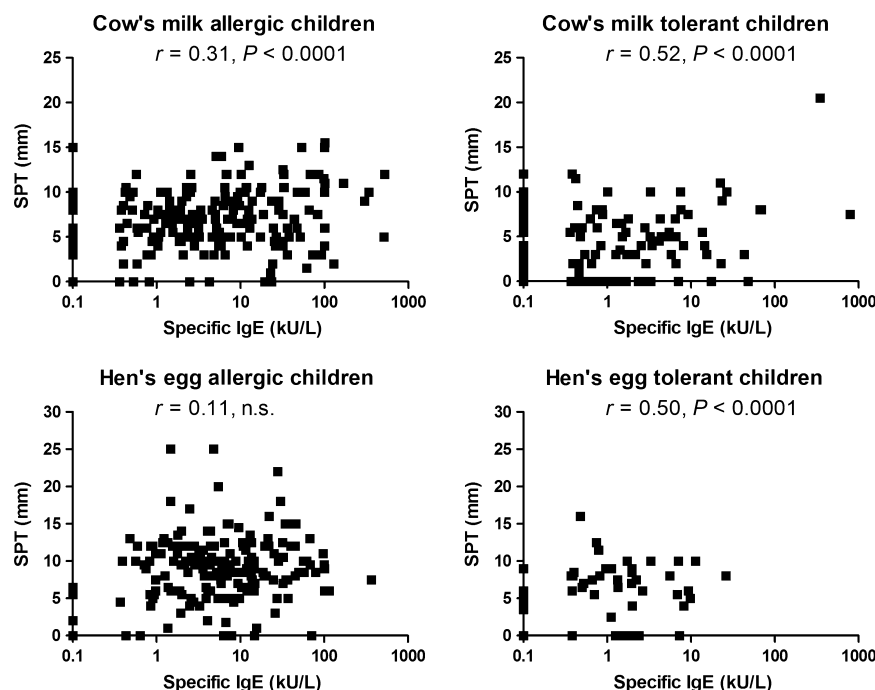


Fig. 1. Relation between weal size of skin prick test (in mm) and specific serum IgE levels (in kU/L) for cow's milk and hen's egg, respectively. The results are shown separately for allergic children (with positive outcome of the oral food challenge test) or tolerant children (negative outcome of the oral food challenge test). Specific IgE below < 0.35 kU/L was set as 0.1 kU/L.

Similar values for sensitivity, specificity as well as positive and negative predictive values have been described for food-specific serum IgE and SPT [40, 48–51]. This is also true for the data presented here, for which these parameters are almost identical to our previously published ones [52]. However, our data indicate that the determination of sensitization in a child with suspected food allergy is highly dependent on the method used. It cannot be stated any longer that SPT or measurement of sIgE may be used interchangeably.

In a small study of 24 grass- and/or tree-pollen-allergic patients and eight control individuals, Niederberger *et al.* studied the association of allergen-specific IgE serum levels with skin and nasal sensitivity using recombinant tree and grass pollen allergens [53]. The authors reported no correlation between sIgE-levels and SPT. Furthermore, in that study weal size of SPT and nasal provocation-severity score correlated significantly, but sIgE-levels and nasal provocation did not.

For both the SPT (*in vivo* test) and sIgE (*in vitro* assay), there may be factors that influence the magnitude of the response such as the number and/or density of IgE epitopes on a particular allergen or the affinity/avidity of IgE antibodies. However, this influence may be different for the two test systems. Furthermore, the presence of specific IgG antibodies may affect the result of the two test systems unequally.

Although it has been shown in several other studies that the SPT is slightly superior to sIgE with regard to specificity and negative predictive values [22, 25, 39, 40, 47, 51], this is notably overridden in this study by the fact of numerous clear instances of opposing results. Transferring our results into the daily clinical practice, a patient evaluated with *in vitro* testing might end up with different advice than a patient who underwent SPT. As neither of the two test systems is superior, the proposed flow sheet may be useful (Fig. 2).

In conclusion, our data show that the correlation between SPT and sIgE is surprisingly low for cow's milk

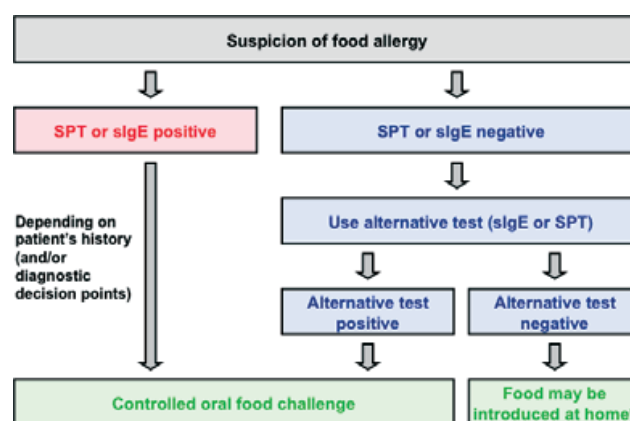


Fig. 2. Decision tree for the diagnostic approach in suspected cow's milk or hen's egg allergy. *In case of any suspicion of a systemic and therefore potentially life-threatening reaction in the history, oral food challenge should be performed under medical supervision.

and hen's egg on an individual basis. Therefore, the tests should not be used interchangeably. Especially in children who receive a negative test result, the alternative test should also be used. However, even if both tests are used, there remain a small proportion of children with a positive oral food challenge without detectable sensitization. Therefore, a comprehensive history is an essential component in evaluating food allergy; in the majority of cases controlled oral food challenges still remain the gold standard in evaluating suspected food allergy in children.

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