

An evaluation of the diagnostic value of different skin tests with egg in clinically egg-allergic children having atopic dermatitis

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Skin testing is a common diagnostic procedure in food allergy, but the final diagnosis of food allergy is based on the clinical response to food challenge. We studied the value of the skin prick-prick test (SPT), skin application food test (SAFT) and atopy patch test (APT) with fresh egg extract in diagnosing egg allergy. Ten clinically egg-allergic children with atopic dermatitis (AD; age 10 months to 8.4 yr, mean 3.4 yr) and 10 egg-tolerant children with and 10 without AD (age 2.4–11 yr, mean 5.5 yr) participated. In SAFT several false-negative reactions were seen, whereas all clinically egg-allergic children were positive in SPT and 40–60% in APT. In APT and in SPT false-positive reactions to egg were observed. In this study comprising a small number of patients including control subjects, neither SAFT nor APT with fresh whole egg extract were able to increase the diagnostic accuracy in detecting egg-allergic children with AD compared with SPT.

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The only accepted methods for verifying the diagnosis of food hypersensitivity are the double-blind, placebo-controlled food challenge (DBPCFC) and open controlled food challenges (OFC) in young children ('gold standard') (1, 2).

Egg allergy is one of the most frequent food allergies among children. Reactions to ingestion of egg are reported to occur almost immediately, representing itching in mouth/throat, rhinitis, conjunctivitis, asthma, urticaria, angioedema, nausea, vomiting, diarrhoea and eventually anaphylaxis. Isolated delayed reactions (i.e. symptoms appearing more than 2 h after ingestion) have, however, also been reported (3).

Different diagnostic *in vivo* and *in vitro* tests are available, but their diagnostic accuracy are not sufficient making them diagnostic tools, often because of poor quality of the extracts used or depending on the technical detection limit of the test. The use of fresh foods for testing has been shown to improve sensitivity and specificity of the tests compared with DBPCFC (4, 5). A positive outcome of a test indicates sensitization, but does

not prove that exposure to the allergen in question causes significant clinical allergic symptoms. Still the diagnosis has to be based on controlled elimination and food challenges (1, 2).

A skin provocation test system for foods, called the skin application food test (SAFT) has been described in studies of small children with atopic dermatitis (AD) (6). It investigates immunoglobulin E (IgE)-mediated acute contact urticaria released by an epidermal application, being more patient friendly because of avoidance of using a needle (7).

The skin prick tests normally used with food allergens investigate type I sensitization, the IgE-mediated reaction, whereas the late reaction might be due to a type IV reaction and thus should be diagnosed by patch testing, normally used for diagnosis of contact dermatitis (3, 8, 9).

Aim: to study the relevance (reliability, reproducibility and safety) of skin prick-prick test SPT, SAFT, and atopy patch test (APT) in clinically egg-allergic children with AD. In

particular, the objective was to determine whether SAFT or APT could increase the diagnostic accuracy in detecting egg allergy.

Material and methods

Patients and control subjects

Ten clinically egg-allergic children with AD (seven girls, three boys) were included in this study. AD was defined by the criteria of Sampson (10) and Hanifin and Rajka (11). Ages ranged from 10 months to 8.4 yr, mean 3.4 yr. All had been challenged with egg (at the Department of Pediatrics or at the Allergy Center, Odense University Hospital) according to the EAACI Guidelines (1) 2–24 months prior to this study, except one suspected of also having Netherton's syndrome. This patient as well as three patients who were challenged more than 1 yr prior to inclusion still had a large SPT to egg, and reported immediate symptoms after accidental intake within the last year. All kept a strict diet avoiding egg and hidden egg according to the dietician's advice. All had histories of immediate reaction to ingestion of egg and two reported delayed symptoms (aggravation of eczema), too. The patients had developed immediate symptoms such as urticaria, flare up of eczema, wheezing, rhinitis, conjunctivitis, facial oedema/erythema and gastrointestinal symptoms, whereas none presented with isolated delayed reactions upon challenge.

Ten egg-tolerant children having AD and a regular intake of egg (four girls, six boys, age 2.4–11 yr, mean 5.3 yr) and 10 egg-tolerant children without AD (normal controls) (five girls and five boys, age 3.6–10.5 yr, mean 5.8 yr) participated as control subjects.

According to the study design, all tests (SPT, SAFT, APT) were performed serially in all children.

Informed consent was obtained from the children's parents, and the study protocol was approved by the local ethics committee of Funen and Vejle counties.

Egg extract and test methods

Fresh whole hen's egg bought locally was used, and sterile saline was used as the negative control. Undiluted fresh whole egg extract was used in SPT and SAFT. In APT, the egg extract was used undiluted and in 25 and 50% dilutions with 0.9% NaCl.

The tests were all applied in duplicate. The skin should be without active eczema or urticaria

treated with group 2 steroids or higher. No topical steroids were used on the arms within 24 h or on the back within a week prior to testing. Other medication was discontinued prior to testing according to recommendations (12) and the EAACI Skin Test Guidelines (13).

Skin prick-prick test

Prick tests were performed in duplicate on the volar surface of the forearm (4, 13). The test was read after 10 min, and the SPT was assessed as positive if the wheal net diameter was 3 mm larger than that of the negative control (0.9% NaCl).

Histamine dihydrochloride 10 mg/ml (ALK-Abelló, Copenhagen, Denmark) was used as positive control.

Skin application food test

The SAFT is based on the mechanism of contact urticaria being a patch test applied for only minutes, and it has recently been found useful in detecting early phase type I immediate hypersensitivity reactions (6). It is regarded a child-friendly test because of no use of a needle and therefore no superficial pain, and it has especially been used in children younger than 3 yr.

The fresh whole egg extract was applied on the volar surface of the forearm using 12 mm Finn Chambers. The test was read after 15 and 30 min. The results were scored as follows: 1 = no reaction; 2 = erythema; 3 = erythema and oedema within the area of the chamber; 4 = erythema and oedema also outside the chamber. A score of 3 or more (7) was regarded as positive.

Atopy patch test

Patch testing is a well-established method of diagnosing allergic contact dermatitis, a delayed type of hypersensitivity (type IV reaction). The major disadvantage of patch testing is that it is less reproducible than other *in vivo* tests because of difficulty in differentiating irritative reactions from true allergic responses.

The APT was performed according to recommendations (ICDRG) described in Textbook of Contact Dermatitis (12). The tests were applied (in duplicate) on the back of the patients using 12 mm Finn Chambers and removed and read after 48 h and read again after further 24 h by the same person. The reactions were classified as negative, doubtful or positive. A doubtful reaction appeared as mild erythema, with no

infiltration, and was regarded as negative. Erythema plus clear infiltration was regarded positive and further classified into three categories: + for erythema and slight infiltration, ++ for erythema, infiltration and papules, and +++ for intense erythema, infiltration and vesicles.

A comparison with the scoring system suggested by Isolauri (8) was also made, i.e. reactions were defined as: negative/irritation/significant erythema/erythema with oedema and eczema. The weakest positive score 'significant erythema (?+)' did not include infiltration according to its definition and therefore it might be interpreted as a negative reaction; consequently calculations were performed in two ways: both considering erythema as a positive and as a negative reaction.

Calculations and statistics

For each group positive reactions were calculated according to guidelines (1, 12, 14). Clinical sensitivity (SE) and specificity (SP), i.e. diagnostic SE and SP, measure the fraction of positive tests among diseased in a study population and the fraction of negative tests among the reference (not diseased) population. Positive predictive value (PPV) was defined as the proportion of clinically allergic individuals among test positives, and negative predictive value (NPV) as the proportion of non-allergic individuals among test negatives. The tests were validated by comparing the outcome to the 'gold standard' DBPCFC or OFC (14).

Discrepant reactions in the duplicate applications and reactions to negative control were excluded from calculations.

Results

The skin tests used were capable of detecting allergic hypersensitivity to egg, but the tests differed in their sensitivity, specificity, safety and reproducibility.

Test outcome

Table 1 shows the diagnostic sensitivity and specificity, and the positive and negative predictive values of SPT, SAFT and APT with fresh whole egg extract.

False-positive results in SPT were seen in 15% (three of 20) with a sensitivity of 100% (10 of 10). Sensitivity of SAFT (at 15 and 30 min) was only 40–50% (two of five, four of eight) but with a high specificity, 100% (19 of 19, 20 of 20). Regarding APT, sensitivity never exceeded 60% (three of five)

in any dilution neither at 48 h nor at 72 h, whereas specificity ranged between 84 and 95% (16 of 19, 18 of 19). Defining erythema without infiltration (doubtful) in APT as positive (8). SE was improved but SP reduced because of an increased number of false-positive reactions (Table 1).

No major difference in SAFT results occurred between application of the egg extract for 15 min compared with 30 min.

Safety of test procedures

Three of 10 patients developed a systemic reaction (erythema, itching, urticaria and/or eczema outside the test area) during or shortly after SAFT testing and required treatment, and consequently thus excluded from further testing with APT. Among the remaining seven patients, one showed severe urticaria and rhinoconjunctivitis shortly after application of APT, and was excluded from further testing. Six patients participated in APT, and the lowest concentration eliciting a reaction in two patients was 25%, one reacted to higher concentrations, one was excluded because of the reaction to negative control, while two showed no reaction at all.

All tests were applied in duplicate to investigate reproducibility. Discordance in the reactions of the double applications with egg are shown in Table 2 together with reliability, i.e. reactions to the negative control (saline). One patient reacted on the negative controls (NaCl) in APT, and discordant reactions in duplicate application were especially seen among the patients concerning SAFT (five patients and one control subject at 15 min, two patients also at 30 min), while among four control subjects in APT, primarily those with AD.

Thus, reproducibility of SAFT and APT were lower than in SPT.

Regarding erythema without infiltration (doubtful) in APT as positive (8) the number of discordant reactions in duplicate application increased as well as reactions to the negative control, especially among the control subjects (Table 2).

The concordances of SPT, SAFT and APT (test outcome compared with gold standard = clinical diagnosis) are listed in Table 3. In our search for the best possible test outcome we determined concordance both using the most sensitive scoring system (regarding a weak reaction as positive) and using a more rigid and correct scoring system, e.g. a doubtful APT was scored as negative. As can be seen, SPT demonstrates in all cases the best concordance followed by SAFT and APT.

Table 1. Diagnostic sensitivity and specificity, and positive and negative predictive values of SPT, SAFT and APT with fresh whole egg

Test	Erythema = negative [SAFT, cut-off $\geq$ score 3; APT, doubtful = negative (*)]				Erythema = positive [SAFT, cut-off $\geq$ score 2; APT, doubtful = positive (†)]			
	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Sensitivity	Specificity	Positive predictive value	Negative predictive value
SPT	100 (10/10)	85 (17/20)	77 (10/13)	100 (17/17)	—	—	—	—
SAFT (min)								
15	40 (2/5)	100 (19/19)	100 (2/2)	86 (19/22)	60 (3/5)	95 (18/19)	75 (3/4)	90 (18/20)
30	50 (4/8)	100 (20/20)	100 (4/4)	83 (20/24)	57 (4/7)	100 (19/19)	100 (4/4)	86 (19/22)
APT (% , h)								
100, 48	60 (3/5)	90 (18/20)	60 (3/5)	90 (18/20)	80 (4/5)	69 (11/16)	44 (4/9)	92 (11/12)
50, 48	60 (3/5)	90 (18/20)	60 (3/5)	90 (18/20)	80 (4/5)	57 (8/14)	40 (4/10)	89 (8/9)
25, 48	40 (2/5)	89 (16/18)	50 (2/4)	84 (16/19)	80 (4/5)	64 (9/14)	44 (4/9)	90 (9/10)
100, 72	60 (3/5)	94 (17/18)	75 (3/4)	89 (17/19)	75 (3/4)	77 (10/13)	50 (3/6)	91 (10/11)
50, 72	60 (3/5)	95 (18/19)	75 (3/4)	90 (18/20)	80 (4/5)	64 (9/14)	44 (4/9)	90 (9/10)
25, 72	40 (2/5)	84 (16/19)	40 (2/5)	84 (16/19)	100 (3/3)	64 (9/14)	38 (3/8)	100 (9/9)

Number of observations shown in parentheses.

*Mild erythema with no infiltration (doubtful reaction) was scored negative (12).

†Mild erythema with no infiltration (doubtful reaction) was scored positive (8).

SPT, skin prick-prick test; SAFT, skin application food test; APT, atopy patch test.

Table 2. Reproducibility and reliability of the tests

	Discordance of reactions in duplicate application			Number of reactions to negative control (NaCl)		
	+egg +AD	—egg +AD	—egg —AD	+egg +AD	—egg +AD	—egg —AD
SPT	0	0	0	0	0	0
SAFT (min)						
15	5 (5)	1 (1)	0 (0)	0 (1)	0 (0)	0 (0)
30	2 (3)	0 (1)	0 (0)	0 (0)	0 (0)	0 (0)
APT (% , h)						
100, 48	0 (0)	0 (0)	0 (1)			
50, 48	0 (0)	0 (1)	0 (2)	1 (1)	0 (0)	0 (4)
25, 48	0 (0)	1 (1)	1 (2)			
100, 72	0 (1)	2 (2)	0 (0)			
50, 72	0 (0)	1 (0)	0 (0)	1 (1)	0 (3)	0 (3)
25, 72	0 (2)	1 (0)	0 (0)			

Number of observations.

+egg +AD, clinically egg-allergic children with atopic dermatitis; —egg +AD, egg-tolerant children with atopic dermatitis; —egg —AD, egg-tolerant children without atopic dermatitis; SPT, skin prick-prick test; SAFT, skin application food test; APT, atopy patch test.

SAFT, cut-off $\geq$ score 3; APT, doubtful reaction (mild erythema without infiltration) = negative. In parentheses: SAFT, cut-off $\geq$ score 2; APT, doubtful reaction (mild erythema without infiltration) = positive.

Discussion

The results of test with non-standard substances must be interpreted with great care to avoid both false-positive and false-negative reactions, and it may also be necessary to test a suitable number of control persons.

If the test is positive in the patient, it has to be demonstrated that the actual test preparation is non-irritant and non-toxic in healthy control subjects, otherwise the observed reaction in the particular patient does not prove allergenicity.

To reduce the need of DBPCFCs several attempts have been made to investigate and

combine different allergologic tests to reliably predict the outcomes of oral food challenges. Some recent studies (3, 6–9, 15–18) have evaluated the use of SAFT or APT (12) in larger groups of children with AD who were suspected of food allergy (the majority) and tested with various food challenges.

In our study the ability of different skin tests to diagnose clinical egg allergy was investigated in a small group of children with egg allergy proven by DBPCFC/OFC. The main purpose was to investigate reproducibility, specificity and safety of the skin tests. The tests were performed with fresh egg extract in both clinically egg-allergic

Table 3. Concordance of test results and clinical diagnosis

Test	Concordance			
	Erythema = negative [SAFT, cut-off $\geq$ score 3; APT, doubtful = negative (*)]		Erythema = positive [SAFT, cut-off $\geq$ score 2; APT, doubtful = positive (†)]	
	Number	%	Number	%
SPT	27/30	90		
SAFT (min)				
15	21/24	88	21/24	88
30	24/28	86	23/26	88
APT (% , h)				
100, 48	21/25	84	15/21	71
50, 48	21/25	84	12/19	63
25, 48	18/23	78	13/19	68
100, 72	20/23	87	13/17	76
50, 72	21/24	88	13/19	68
25, 72	18/24	75	12/17	71

Those with discordance in reactions and those with a reaction to negative control were excluded.

*Mild erythema with no infiltration (doubtful reaction) was scored negative (12).

†Mild erythema with no infiltration (doubtful reaction) was scored positive (8).
SPT, skin prick-prick test; SAFT, skin application food test; APT, atopy patch test.

children with AD and in egg-tolerant children with and without AD.

SPT and SAFT

Skin prick-prick testing was performed like in routine but using undiluted fresh whole egg extract. It identified all DBPCFC-positive patients, and showed high concordance with the clinical diagnosis. The results suggest that SPT is an acceptable method of excluding immediate food allergy (NPV: 100%) and a suggestive positive indication of clinical hypersensitivity (PPV: 77%).

Few studies, and all from the same research group, have focused on the predictive ability and diagnostic relevance of SAFT. In a study by Oranje et al. (6), children with AD suspected of egg, milk or peanut allergy were investigated with repetitive SAFT within 1 yr. The foods were applied in the same form in which they were consumed. Open oral challenges were only performed in case of discrepancies between the clinical history and SAFT results. They concluded that SAFT was more frequently positive in AD children aged 0–2 yr than in older children and that the test was highly reproducible, the agreement between duplicate testing of SAFT was $\geq 88\%$.

In another study of children with AD and suspicion of food allergy (milk, egg, peanuts)

performed by de Waard-van der Spek et al. (7) a good correlation between SAFT and SPT and oral challenges was found. With a SE of 83% (19 of 23), SP of 100% (41 of 41), PPV of 100% (19 of 19), and a NPV of 91% (41 of 45) the test appeared to be a reliable skin test for evaluating food allergy in children younger than 4 yr having AD. They found a good agreement between outcome of the SAFT and the prick-prick test using fresh food, and concluded that SAFT ought to be performed in children < 3 yr whereas prick-prick test should be performed above this age. In our study, six patients < 3 yr of age participated: two had a positive reaction in SAFT at the 30 min reading, one was positive at both 15 and 30 min, and the remaining three patients either had discordant reactions in the duplicate application or were negative.

Selected children with AD and suspected food allergy were recruited into the study by de Waard-van der Spek et al. (7). The study did not include healthy children, who however had been investigated in a previous study from the same group and found negative, as was the case in this study (19).

We were unable to confirm the previous findings in our group of challenge proven egg-allergic children – sensitivity was only 40–50%.

The fact that severe reactions were seen due to SAFT (three of 10) in our study makes the test under these conditions questionable – we read the reactions after 15 and 30 min in contrast to the guidelines suggested by Oranje et al. (intervals of 10 min, maximum time 30 min) (6), but in all three cases of systemic reactions the altered reading time could not explain the severe reaction: in one patient the SAFT was terminated already after few minutes application because of systemic reaction, whereas in the remainder two cases, one was negative at the 15 min reading and developed a systemic reaction 20 min later and the final patient was inconclusive at the 15 min reading and developed a systemic reaction 45 min later.

Finally, reproducibility of SAFT was insufficient as discordant findings were obtained in nearly half of the patients – SAFT has not been investigated using double determinations previously.

As SPT with the same egg preparation demonstrated a SE of 100%, it is unlikely that the false-negative reactions in SAFT are due to the test material itself, although the use of unstandardized extracts always carry a risk of variability. Changing the cut-off, i.e. regarding isolated erythema as positive did not influence the outcome of the test.

APT

In some studies the properties of prick testing and atopy patch testing have been reported (3, 8, 15, 16). In a study by Isolauri (8) only children (2–36 months of age, mean 14 months) having AD participated and no healthy control subjects without AD were included. They found that most children with immediate reactions to DBPCFC with cow's milk had positive reactions to skin prick test but not to patch testing, whereas a major part of those with late reactions after challenge had positive patch test reactions and fewer positive immediate reactions in the skin. SE of atopy patch testing was 61%. After all they conclude that the most accurate method of diagnosing food allergy in infants with AD is the controlled challenge procedure.

In the classification of the APT outcome in that study (8), the reaction 'significant erythema (?+)' was used without further definition. This reaction seemed to be regarded positive although not including infiltration. Normally such reaction would be classified as doubtful/negative.

In our study we made calculations where the reaction 'doubtful (mild erythema)' was interpreted identical to the scoring system suggested by Isolauri (8), i.e. scored positive. Using this cut-off did not improve the outcome. The number of false-positive reactions among the control subjects increased, revealing a lower positive predictive ability, and furthermore a decrease in reproducibility was seen (Tables 1 and 2).

In a recent study by Strömberg (16) the APT was found to be a more sensitive method than skin prick test in diagnosing food allergy in children (the majority <2 yr of age, mean 16 months) with atopic eczema. Children with suspected food allergy (immediate reactions) but without atopic eczema were not included. SE/SP of APT was 71/97% and of skin prick test 60/97% for egg.

A study by Niggemann et al. (3) investigated the value of APT in diagnosing food allergy in 75 children (4 months to 12.5 yr, median age 2.1 yr) having AD. Food provocations with cow's milk, egg, wheat and soybean were performed and the atopy patch testing was described as a useful diagnostic tool with a SE of 55%. Six children could not be included because of clinical reactions with acute local urticaria and itching (contact urticaria) 5–15 min after administering the APT, all with egg allergen.

In another study from the same group (17), the APT result was positive in 57% of cases of challenge-proven egg allergy while skin prick test was positive in 89%. APT was found to have a

PPV of 94%, and skin prick test 81%. The performance of APT in predicting early or late-phase reactions was identical.

In a study of suspected food allergy in 139 children with AD (2 months to 11.2 yr, median 13 months) performed by Niggemann et al. (18), it was concluded that the age of the children had no influence on the outcome of the APT, and furthermore the APT results showed no statistically significant difference between early or late clinical reactions.

Vanto et al. (9) investigated the performance of APT in 301 infants with suspected cow's milk allergy (aged <1 yr, and 74% having AD). Using the same patch test method, they could not confirm Isolauri's results of patch testing (8): infants with immediate, delayed, or negative challenge reactions showed consistent distributions of APT reactivity. Furthermore, they observed that the APT was slightly irritating the skin, causing erythema also when control APTs were performed. They found a PPV of 40% and SE of 18% using APT (skin prick test: 79% and 69%, respectively). Because of positive reactions to control APTs and reactions in challenged negative subjects the APT could not be recommended as an effective diagnostic tool.

However, these investigations (3, 8, 9, 15–18) reveal no information about the diagnostic sensitivity and specificity of the APT because of the lack of suitable control subjects, i.e. non-allergic healthy children without AD, because they only used challenge negative AD patients as controls. In two studies comprising 75 and 183 patients (3, 8) pilot investigations were made using six to eight persons without AD who were tested negative in APT (12). We found no reactions in control subjects without AD but in total five egg-tolerant children with AD who reacted. Three of the AD control subjects had a positive SPT, two of those also had a positive reaction in APT together with two others (two at 48 h, one of those and two others at 72 h, different concentrations). Furthermore, discordant reactions in duplicate applications were prevalent among control subjects with AD (Table 2).

The use of APT shows conflicting results which might be due to selection of study group, different definitions of delayed reactions, non-standardized allergen extract, and interpretation of doubtful/erythematous reactions on the skin.

According to recommendations (13) well-documented methods with documented reproducibility and standardized allergens with a well-defined potency and documented diagnostic effect should

be used. This would improve quality of studies made and facilitate comparison between data obtained from different research groups.

As we have never diagnosed isolated late-phase reactions to DBPCFC/OFC with egg or other foods in children with AD, such patients could not be included in this study. Among the clinically egg-allergic children with immediate reaction after egg challenge 40–60% showed reaction in APT, the test investigated for predicting delayed clinical reactions. The test does not seem clinically relevant because of positive reactions in egg-tolerant children with AD. Furthermore, one of seven tested in APT showed a severe systemic reaction shortly after application of the test.

Although only few patients were included in our study, the value of the skin tests could be described and evaluated because of systemic reactions among patients as well as reactivity among control subjects with and without AD.

No advantage of the APT or SAFT in diagnosing egg allergy was found due to lack of reproducibility and reliability. Compared with SPT, SAFT and APT resulted in systemic reactions and were less reproducible whereas APT had a lower demonstrated SE and PPV. None of the tests had any superiority to SPT.

Still the DBPCFC/OFC remain the gold standard for diagnosing clinically relevant food allergy.

Conclusion

Several false-negative reactions were seen using SAFT and APT, and false-positive reactions to egg also in APT. Systemic reactions occurred in both SAFT and APT.

In this study comprising a small number of patients and including control subjects, neither SAFT nor APT with fresh whole egg extract were able to increase the diagnostic accuracy in detecting egg-allergic children with AD compared with SPT.

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