

Skin prick test to egg white provides additional diagnostic utility to serum egg white-specific IgE antibody concentration in children

Adina Kay Knight, MD,^a Wayne G. Shreffler, MD, PhD,^b Hugh A. Sampson, MD,^b
Scott H. Sicherer, MD,^b Sally Noone, RN, MSN,^b Shideh Mofidi, MS, RD, CSP,^b
and Anna Nowak-Wegrzyn, MD^b New York, NY

Background: Levels of IgE antibody to egg white of greater than 7 kIU/L are highly predictive of clinical reactivity to egg, and lower levels often require evaluation with oral food challenge (OFC) to establish definitive diagnosis. OFCs have inherent risks, and diagnostic criteria indicating high likelihood of passing would be clinically useful.

Objective: We sought to determine whether the size of the skin prick test (SPT) to egg white adds diagnostic utility for children with low egg white-specific IgE antibody levels.

Methods: A retrospective analysis of clinical history, egg white-specific IgE antibody levels, SPT responses, and egg OFC outcomes was performed.

Results: Children who passed ($n = 29$) egg OFCs and those who failed ($n = 45$) did not differ significantly in age, clinical characteristics, or egg white-specific IgE levels. There were, however, significant differences between both egg white SPT wheal response size and egg/histamine SPT wheal index.

Children who failed egg OFCs had a median wheal of 5.0 mm; those who passed had a median wheal of 3.0 mm ($P = .003$). Children who failed egg OFCs had a median egg/histamine index of 1.00; those who passed had a median index of 0.71 ($P = .001$). For egg white-specific IgE levels of less than 2.5 kIU/L, an SPT wheal of 3 mm or an egg/histamine index of 0.65 was associated with a 50% chance of passing.

Conclusion: In children with low egg white-specific IgE levels, those with smaller SPT wheal responses to egg were more likely to pass an egg OFC than those with larger wheal responses. The size of the egg white SPT response might provide additional information to determine the timing of egg OFC.

Clinical implications: The size of the egg white SPT wheal response might provide the clinician with additional information to determine the timing of egg OFC in children

with low egg white-specific IgE antibody levels. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Egg allergy, food allergy, oral food challenge, skin prick test

Cow's milk, egg, and peanut allergy are the 3 most common IgE-mediated food allergies in children.¹ The estimated prevalence of egg allergy is 1.6% in 2-year-old children.^{2,3} Egg allergy is associated with atopic dermatitis and an increased risk of asthma.⁴⁻⁶ Recent studies reported doubling of peanut allergy prevalence in young children in the past 2 decades,^{7,8} and clinical observations indicate that a similar trend also might be true for other food allergies, including egg allergy. The majority of children with egg allergy become egg tolerant by school age, and it is important to determine the earliest appropriate time to attempt to introduce or reintroduce egg into the diet.⁹⁻¹¹ Avoidance of egg is difficult because of its ubiquitous presence in prepared foods. Egg avoidance is stressful and also might lead to nutritional deficiencies if associated with other food allergies. Therefore it is desirable to perform periodic testing to determine whether an egg allergy has resolved.

The current diagnostic approach includes a thorough history with skin prick tests (SPTs) to egg white and measurement of serum egg white-specific IgE antibody levels. A clinically suggestive history of food allergy can only be confirmed in about 50% of cases.¹² SPTs and serum IgE levels assist in the diagnosis, but there are false-positive results, especially in highly atopic children.¹² The current gold standard for the diagnosis of food allergy remains the double-blind, placebo-controlled oral food challenge (DBPCFC).¹ These challenges must be performed in medically supervised settings with treatment for severe reactions readily available, making them both costly and limited in availability.

Previous work has shown that serum food allergen-specific IgE antibody levels can be used to determine the likelihood, although not the severity, of a reaction.^{13,14} Serum egg white-specific IgE antibody levels of greater than 7 kIU/L in older children and 2 kIU/L or greater in infants younger than 2 years are more than 95% predictive of clinical reactivity.^{15,16} However, the clinical

From ^athe Department of Medicine, Division of Clinical Immunology, and ^bthe Department of Pediatrics, Division of Allergy and Immunology, Jaffe Food allergy Institute, Mount Sinai School of Medicine.

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Reprint requests: Anna Nowak-Wegrzyn, MD, Pediatric Allergy and Immunology, Department of Pediatrics, Box 1198, Mount Sinai School of Medicine, One Gustave Levy Place, New York, NY 10029. E-mail: anna.nowak-wegrzyn@mssm.edu.

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Abbreviations used

DBPCFC: Double-blind, placebo-controlled oral food challenge
 OFC: Oral food challenge
 SPT: Skin prick test

significance of lower egg white–specific IgE levels requires evaluation with OFCs. Previous studies reported that approximately 10% to 40% of children suspected to have food hypersensitivity caused by a history or positive SPT reactions with undetectable food–specific IgE antibody react to the ingestion of the offending food.^{14,17,18} Several investigators looked at the positive predictive value of an SPT for most common food allergens, such as cow's milk, egg, and peanut, and found higher chances of failing OFCs with larger SPT wheal responses.^{14,18–21} Because OFCs have inherent risks, including anaphylaxis, additional diagnostic criteria to identify patients most likely to pass an OFC would be extremely useful in clinical practice.^{22,23} We sought to determine whether SPTs can differentiate children with low egg white–specific IgE levels who pass an oral egg challenge from those who fail.

METHODS

We performed a retrospective analysis of serum egg white–specific IgE antibody levels, SPT results, and oral egg challenge outcomes of children with egg allergy. Cases were identified through the General Clinical Research Center database and outpatient billing records from April 2001 through November 2004. Typically, children were selected for oral challenge on the basis of low egg white–specific IgE levels (≤ 2.5 kIU/L) and lack of any known recent egg-associated allergic reactions. Children with egg white–specific IgE levels of greater than 2.5 kIU/L were challenged if they presented with a recent history of tolerating small amounts of egg or participated in another study protocol requiring an OFC to egg.

SPTs were performed with a sterile bifurcated needle (Precision Medical Products, Inc, Denver, Pa), commercial egg white extract (Greer Laboratories, Inc, Lenoir, NC), and a negative saline and positive histamine control. The size of the skin test response was calculated as a mean of the longest diameter and its longest orthogonal measured at 10 to 15 minutes. To control for the variability of SPTs that might result from the use of different SPT devices and techniques, we also report the ratio of the size of the egg wheal to the histamine wheal, presuming that any differences in wheal size caused by the device or technician should be similar and thus not affect the ratio.^{21,24}

Serum egg white–specific IgE antibody concentrations were measured with the Pharmacia CAP System (Pharmacia Diagnostics, Uppsala, Sweden); the lower limit of detection is 0.35 kIU/L.

DBPCFCs were conducted in the Mount Sinai General Clinical Research Center, as previously described.²² Briefly, during the active portion of a challenge, 10 g of lyophilized egg white (Deb-El Foods, Elizabeth, NJ) mixed in a masking food was administered in gradually increasing doses every 10 to 15 minutes over 90 minutes. The initial dose was 10 to 100 mg (0.1% to 1% of total amount of 10 g). Outpatient OFCs were conducted in an open manner under physician observation and with emergency medications available and typically involved a serving of French toast made with one whole egg that was

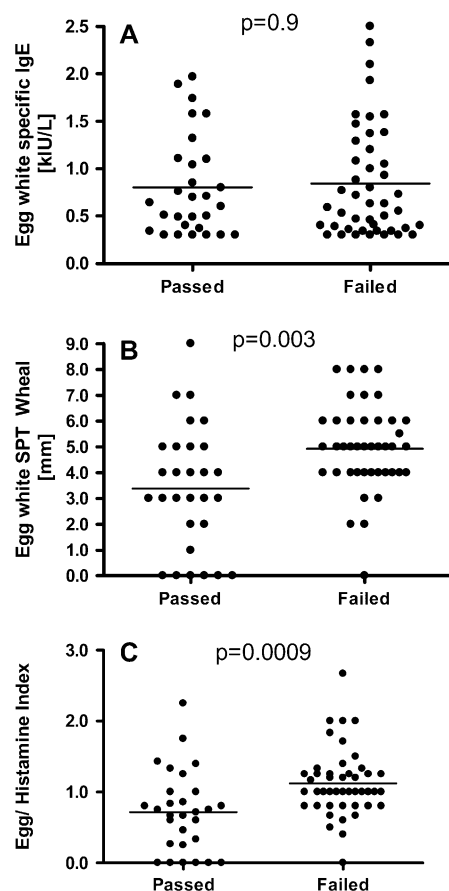


FIG 1. Comparisons between children with egg allergy who passed and those who failed egg OFCs in regard to egg white–specific IgE level (A), egg white SPT wheal response size (B), and egg/histamine index (C).

administered over 1 hour.²⁵ Open challenges that elicited only subjective symptoms were followed up by evaluation with a DBPCFC.

Age at challenge, sex, history of prior reaction to egg, asthma, eczema, allergic rhinitis, oral allergy syndrome, family history of food allergy, and family history of any allergy were analyzed for differences between the children who passed compared with those who failed oral egg challenges. Statistical analysis was performed with the 2-tailed Mann-Whitney test, the Fisher exact test, and Spearman rank correlation (Prism, Graph Pad Software, Inc, San Diego, Calif). Logistic regression was performed with SAS software, and probability formulas were plotted with SigmaPlot 2004 (9.01; Systat Software, Inc, Port Richmond, Calif).

Informed consent was obtained from the participants, and the study was approved by the Institutional Review Board of Mount Sinai School of Medicine in New York, NY.

RESULTS

Eighty-nine oral egg challenges in 78 children were identified. Six patients with egg white–specific IgE antibody levels of greater than 2.5 kIU/L were excluded from the analysis because they were challenged under a specific research protocol and were not representative of the general population of patients with egg allergy undergoing OFCs.

TABLE I. Comparison of laboratory and clinical characteristics between children who passed and those who failed OFCs to egg (n = 74)

	Pass	Fail	P value
n	29	45	
Mean age (range), y	5.1 (1.9-14.6)	5.7 (2.1-13.6)	.2
Male sex, %	66	58	.6
Female sex, %	34	42	
Median egg white-specific IgE level (range), kIU/L	0.64 (<0.35-1.97)	0.63 (<0.35-2.50)	.9
Median egg white wheal (range), mm	3.0 (0-9)	5.0 (0-8)	.003*
Median egg white flare (range), mm	12.0 (0-44)	20.0 (0-44)	.002*
Median egg/histamine index (range)	0.71 (0-2.3)	1.00 (0-2.7)	.0009*
Past clinical reactivity to egg, %	59	69	.5
Other food allergies, %	90	91	1.0
Asthma, %	55	71	.2
Eczema, %	79	89	.3
Allergic rhinitis, %	55	82	.02*
Oral allergy syndrome, %	3	4	1.0
Family history of food allergy, %	28	36	.6
Family history of any allergy, %	86	89	.7

*Statistically significant: $P < .05$.

An additional 9 patients were excluded because of incomplete records. Sixty-eight of these challenges were DBPCFCs conducted between April 2001 and April 2005 in the General Clinical Research Center. The remaining 12 challenges were conducted in the outpatient clinic. Only one outpatient challenge result was positive: the child had no history of atopic dermatitis and tolerated the full challenge dose before development of a macular rash behind the left ear. Nine children underwent more than one OFC to egg. In all cases challenges were conducted at least 6 months apart, and children had separate measurements of egg white-specific IgE levels and egg SPTs before each OFC; therefore each of the multiple OFCs in an individual child was considered as an independent event in the final analysis.

Children who passed (n = 29; 39%) the oral egg challenge and those who failed (n = 45; 61%) were not different with respect to age, egg white-specific IgE concentration (Fig 1, A), or clinical characteristics, except for allergic rhinitis. There were, however, statistically significant differences between egg white SPT wheal-and-flare responses and egg/histamine SPT indices (Fig 1, B and C, and Table I).

Children who failed their oral egg challenge had a median wheal of 5.0 mm (range, 0-8 mm) compared with those who passed, who had a median wheal of 3 mm (range, 0-9 mm; $P = .003$; Fig 1, B). Table II depicts the observed odds of passing the OFC on the basis of egg white SPT wheal response size. Logistic regression analysis of the SPT wheal response size and OFC outcome estimated the probability of passing an oral egg challenge for a specific wheal diameter as $y = 1 - [1 / (1 + \exp(1.213 - 0.395 * \text{Wheal}))]$, which is presented graphically in Fig 2, A. On the basis of this model, if the wheal was equal to 3 mm, 50% of such selected children would be expected to pass their oral egg challenges (Fig 2, A).

TABLE II. Chances of passing an OFC to egg with different egg white SPT response

Egg white SPT wheal response (mm)	Total no.	Passed OFC (%)	Failed OFC (%)	Odds of passing
0	7	6 (85.7)	1 (14.3)	6
1	1	1 (100)	0 (0)	*
2	4	2 (50)	2 (50)	*
3	8	6 (75)	2 (25)	3
4	19	5 (26.3)	14 (73.7)	0.36
5	15	4 (26.7)	11 (73.3)	0.36
6	10	2 (20)	8 (80)	0.25
7	5	2 (40)	3 (60)	0.67
≥8	5	1 (20)	4 (80)	0.25

*Odds were not calculated because of a small number of observations.

Children who failed their oral egg challenges had a median egg/histamine SPT index of 1.0 (range, 0-2.67), and those who passed the egg challenge had a median egg/histamine SPT index of 0.71 (range, 0-2.25; $P = .001$; Fig 1, C). Table III depicts the observed odds of passing the OFC on the basis of egg/histamine SPT index. Logistic regression analysis of the egg/histamine SPT index and outcome of oral egg challenge was used to estimate the probability of passing a challenge as $y = 1 - [1 / (1 + \exp(1.120 - 1.712 * \text{Index}))]$. On the basis of this model, if the egg/histamine SPT index was equal to 0.65, 50% of such selected children would be expected to pass their oral egg challenges (Fig 2, B).

There were no significant differences between the children who passed oral egg challenges and those who failed on the basis of sex, history of previous reactions to egg, asthma, eczema, oral allergy syndrome, or family history of any allergy (Table I). There was a significant increase in the diagnosis of allergic rhinitis in children who failed oral egg challenges compared with those who

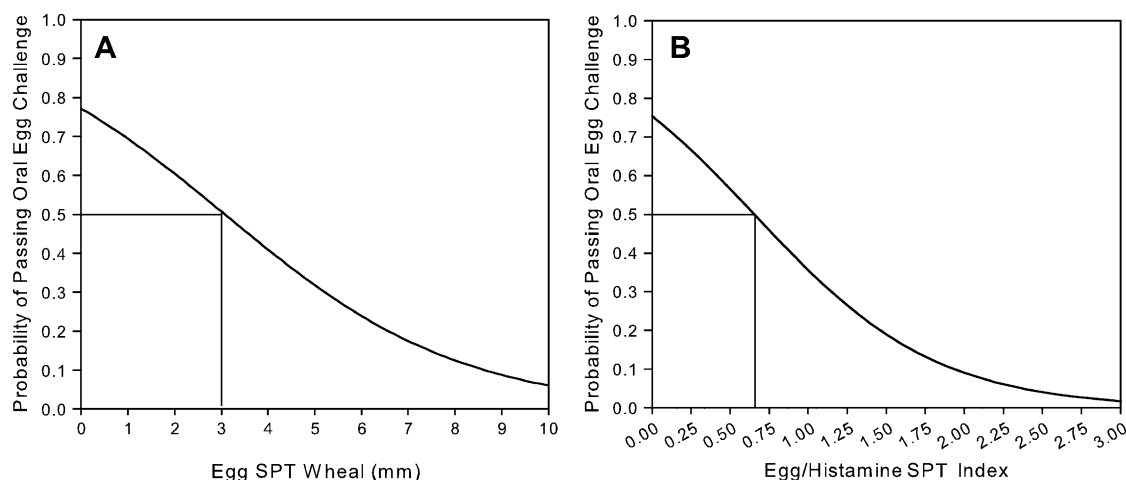


FIG 2. Predicted relationship between egg white SPT wheal response size and oral challenge to egg (50% passing rate with egg white wheal response of 3 mm; **A**) and egg/histamine index and oral challenge to egg (50% passing rate with index of 0.65; **B**).

TABLE III. Chances of passing an OFC to egg with different egg/histamine index

Index	Total no.	Passed OFC (%)	Failed OFC (%)	Odds of passing
0-0.25	8	7 (87.5)	1 (12.5)	7
0.26-0.5	5	3 (60)	2 (40)	1.5
0.51-1	35	13 (37)	22 (63)	0.6
>1	26	6 (23)	20 (77)	0.3

passed (82% vs 55%, $P = .02$). The significance of this is unclear, although there is a general trend toward failure of oral egg challenge with increased number of atopic diagnoses and older age at challenge.

The only child who failed the oral egg challenge with both an egg white–specific IgE level of less than 0.35 kIU/L and an egg white SPT wheal response of 0 mm tolerated the entire challenge dose and then had urticaria during the placebo portion of the DBPCFC given 2 hours later. This child continued to avoid egg in his diet and declined a repeat challenge. The other 9 children who failed the oral egg challenge with undetectable (<0.35 kIU/L) levels of egg white–specific IgE had egg white SPT wheals from 4.0 to 6.0 mm and egg/histamine SPT indices from 0.67 to 1.71.

During failed oral egg challenges, cutaneous symptoms (urticaria, angioedema, pruritus, erythema, and rash) were reported in 71%, gastrointestinal symptoms (nausea, emesis, abdominal pain, and diarrhea) in 27%, upper respiratory tract symptoms (sneezing, nasal congestion, and rhinorrhea) in 24%, and lower respiratory tract symptoms (cough, wheezing, and shortness of breath) in 2%. No child experienced severe respiratory symptoms or decrease in blood pressure. Twenty-eight percent of reactions involved 2 or more organ systems. Forty-four of

the 45 children who failed oral egg challenges were treated with oral diphenhydramine, and 3 (7%) required treatment with intramuscular injection of epinephrine.

Five children reacted to the first challenge dose given (1% or 100 mg egg protein), including one child who was treated with epinephrine. Of these, 4 of the 5 had a previous history of reacting to egg; however, only 2 had a history of a previous generalized reaction, including the one requiring epinephrine during challenge. In addition, 2 other children reacted with generalized symptoms requiring epinephrine. One of these children reacted after 30% of the dose and had no history of clinical reactivity to egg, and the other reacted after 55% of the dose and had a history of contact urticaria to egg. Thus of the 3 children requiring epinephrine for generalized reactions during the challenge, one had no previous history of clinical egg reactions and had been avoiding egg successfully on the basis of positive test results (positive SPT response and detectable egg white–specific IgE levels).

We were interested in determining whether there were any features specific to children who either had reacted to very low doses of egg protein or experienced generalized reactions that required epinephrine that would differentiate them from children who passed the OFC, thus enabling exclusion of this group from the risks of oral challenge. Comparison of children in this high-risk group ($n = 15$) with all children who passed the egg challenge ($n = 29$) showed no statistically significant differences in egg white–specific IgE levels or clinical characteristics. To further look for differences between this high-risk group and a group that passed OFCs with similar SPT responses and egg/histamine indices, we compared children who failed ($n = 15$) with those who passed despite an egg white SPT wheal response of 5.0 mm or greater ($n = 9$); however, there were still no statistically significant differences to identify children at high risk (mean age: fail, 6.4 years

vs pass, 8.0 years [$P = .2$]; median egg white–specific IgE level: fail, 0.63 kIU/L vs pass, 0.64 kIU/L [$P = .9$]; prior clinical reactivity: fail, 80% vs pass, 56% [$P = .2$]; asthma: fail, 67% vs pass, 100% [$P = .1$]), and all children in both groups had a history of other food allergies. There were no significant correlations between egg challenge dose tolerated or severity of reaction and egg white–specific IgE level, egg white SPT wheal response diameter, egg SPT wheal/histamine index, history of prior reaction, asthma, or other food allergies (Spearman rank correlation).

For completeness, we repeated our analyses using all 80 eligible OFC records, including those for 6 children with egg–specific IgE levels of greater than 2.5 kIU/L, and found very similar results (data not shown).

DISCUSSION

DBPCFC remains the gold standard for the diagnosis of food allergy. Previous studies have focused on determining the positive predictive values of serum food allergen–specific IgE antibody levels and SPT wheal response diameters in regard to positive OFC outcomes.^{13,15,20,21,26,27} Our goal was to investigate whether there is added diagnostic value in performing SPTs in children with egg allergy and low serum egg white–specific IgE concentrations. We found that in children with low serum egg white–specific IgE antibody levels (<2.5 kIU/L), SPT mean wheal response diameters of 3 mm or egg/histamine indices of 0.65 predicted a 50% rate of passing an egg OFC. However, the likelihood of passing an egg challenge was highest when the egg white SPT wheal response diameter was less than 3 mm (considered a negative test result) and when the egg/histamine index was less than 0.25. Our results indicate that egg white SPT wheal response size and egg/histamine index might be clinically useful diagnostic criteria for selecting children most likely to pass an egg challenge.

Can we apply our results to a general population of children with egg allergy? Children in our study likely represent the more severe phenotype, the more persistent phenotype, or both of egg allergy because the majority of children had multiple food allergies, as well as other atopic diseases, such as atopic dermatitis, asthma, and allergic rhinitis. Accordingly, it is not surprising that our oral egg challenge failure rate of 62% is higher than the 42% recently reported by Perry et al.²³ However, because children were carefully selected to have low egg–specific IgE antibody levels and no recent clinical reactivity to egg, the 10% rate of multisystem reactions is lower than the 28% rate previously reported.²² An additional explanation for the lower rate of multisystem reactions might be the low initial dose of egg administered. Considering the potential selection bias toward more severe egg allergy, the proposed cutoff values for egg white wheal response and egg/histamine index might be expected to be more conservative than those generated in a general population of children with less severe egg allergy. Nevertheless, our results

must be confirmed in a more diverse population with food allergy, including more patients with isolated egg allergy, for general applicability. We also plan to validate current results with a prospective analysis of the results of egg DBPCFCs.

Our study population includes children with low egg white–specific IgE levels and is not likely to be applicable in children with higher egg white–specific IgE levels. Because our population was selected on the basis of low egg white–specific IgE levels, this probably accounts for the similar egg white–specific IgE levels between those passing and failing the oral challenge. Also, with the challenge population preselected on the basis of low egg white–specific IgE level, the study was not powered to see small differences in egg white–specific IgE levels between the 2 groups. Alternatively, our results might suggest that at lower egg white–specific IgE levels, functional characteristics of IgE antibody (eg, avidity), presence of blocking antibodies, or presence of inhibitory receptors on mast cells and basophils might be more relevant than IgE level and better evaluated with a bioassay, such as a SPT.

Considering that real-life variability of skin testing might be greater than that seen in our institution, proposed guidelines for cutoff sizes of egg white–induced wheal responses should be approached with caution. In that regard a standardized egg/histamine index might be more applicable as a parameter for selecting children for OFCs to egg in general allergy practice.

In children with low egg white–specific IgE levels, those with smaller SPT wheal responses to egg white were more likely to pass their oral egg challenge than those with larger SPT reactions. The size of the egg white SPT response might provide the clinician with additional information to determine the best timing for oral egg challenge. Children with a low egg white–specific IgE level but a large SPT wheal response to egg white might benefit from deferring a challenge for another 6 months to a year and having a repeat evaluation before an oral egg challenge. Additionally, children with both a low egg white–specific IgE level and a small SPT response to egg white might undergo egg challenge with less anxiety on the part of the family.

Although helpful in determining the likelihood of passing an oral egg challenge, the SPT did not provide any absolute cutoffs. Some children with small SPT responses to egg white reacted to egg during challenge, and some children with large SPT responses passed their oral egg challenge. The lack of any severe reactions and a high pass rate in children with both undetectable egg white–specific IgE levels and very small egg white SPT wheal responses with or without a prior history of clinical reactivity to egg should encourage oral challenges in this population.

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