

Relationship between oral challenges with previously uningested egg and egg-specific IgE antibodies and skin prick tests in infants with food allergy

Carlo Caffarelli, MD,^a Giovanni Cavagni, MD,^b Salvatore Giordano, MD,^a Ivana Stapane, MD,^a and Clementina Rossi, MD,^a Parma and Brescia, Italy

Background: Positive skin prick test (SPT) and RAST reactions to egg that had never previously been ingested have been observed in infants with food allergy. The likelihood of having clinical hypersensitivity reactions when egg is first ingested and the predictive value of SPT and RAST remain to be elucidated.

Objective: We investigated the relationship between egg-specific IgE antibodies and positive SPT reaction to egg, and the development of clinical hypersensitivity on the first exposure, in infants with food allergy.

Methods: The patient group consisted of 21 infants with food allergy and positive SPT and/or RAST reaction to egg, which they had never previously ingested; the control group of 12 infants had food allergy and negative test results. All subjects underwent double-blind placebo-controlled food challenges with egg.

Results: Thirteen of 21 patients (61%) and one of 12 control subjects (8%) had positive reactions to challenges ($p < 0.01$). Thirteen positive reactions to challenges (93%) elicited immediate symptoms. Late-onset eczema occurred in two children. SPT results showed a high sensitivity (0.92) and negative predictive accuracy (0.92), whereas specificity (0.57) and positive predictive accuracy (0.61) were poor. RAST did not have any diagnostic advantage over SPT.

Conclusions: In infants with food allergy SPT with egg may be helpful in predicting which patients will react to the first exposure. (*J ALLERGY CLIN IMMUNOL* 1995;95:1215-20.)

Key words: Infants, food allergy, oral food challenge, uningested egg, skin prick test, RAST

In infants with food allergy^{1,2} and a high risk of allergic disorders,³⁻⁵ a late introduction of highly allergenic foods such as egg, into the diet has been suggested to prevent sensitization. Nevertheless, in such infants the appearance of a positive skin prick test (SPT) reaction to egg⁶⁻⁹ and egg-specific IgE antibodies^{5-8, 10, 11} has been documented.

The likelihood of these infants having reactions when they first receive egg, and the usefulness of SPT and RAST as predictors, remain to be elucidated. Infants with positive SPT¹² and RAST reactions⁵ to egg have been sparsely documented to

Abbreviations used

DBPCFC:	Double-blind placebo-controlled food challenge
SPT:	Skin prick test

react on the first exposure. The disappearance of positive SPT¹³ and RAST reactions⁶ to egg has been reported among infants without signs of atopic disease.

Double-blind placebo-controlled food challenges (DBPCFC), SPT, and RAST to egg, which had never been previously ingested, were performed in infants with food allergy, to determine whether the results of immunologic tests correlated with the development of clinical hypersensitivity reactions.

From ^aDepartment of Pediatrics, University of Parma, and ^bDepartment of Pediatrics, University of Brescia.

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Reprint requests: Carlo Caffarelli, MD, Clinica Pediatrica, Via Gramsci 14, 43100 Parma, Italy.

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TABLE I. Age, sex, symptoms, and SPT and RAST results to offending food as suspected by history, and SPT and RAST reactions to previously uningested food in the patient group

Case No.	Age (mo)/sex	Offending food			Symptoms	Egg	
		Food	Prick test	RAST score		Prick test	RAST score
1	24/M	Milk	+	1	E	++++	2
2	19/F	Milk	+	2	E, U, A	++	3
3	22/F	Milk	++++	3	U, V, H, M, D, A	++	0
4	19/M	Wheat	++	2	E	++	2
5	15/M	Milk	++	1	E	++	0
6	26/M	Rice	+	2	E	++++	4
		Wheat	+	3	E		
7	24/F	Citrus	—	0	E	+	0
		Tomato	—	0	E		
8	19/F	Egg	++	2	E, S, U, A	++	3
		Wheat	++	2	E		
9	25/M	Potato	—	2	E	—	2
10	44/M	Milk	++	3	E	++	3
11	45/M	Wheat	—	2	E, U, A, S	++++	3
		Milk	++	2	E, U		
12	13/M	Milk	++	0	E	++	1
13	17/F	Milk	+	0	E	+++	0
14	40/M	Milk	++++	4	E, U	+++	3
		Wheat	—	3	E		
15	39/F	Milk	—	0	E	++++	2
16	5/M	Milk	—	0	U	+++	2
17	26/M	Milk	++	4	E, U	+++	4
		Wheat	+	3	E, U		
		Pork	++	3	E, U		
18	20/F	Cod	—	0	E	++	2
19	24/M	Milk	—	0	E	++++	3
20	20/M	Milk	—	0	E	++++	3
21	13/F	Milk	++	2	E	++	1

A, Angioedema; D, diarrhea; E, eczema; H, hematemesis; M, melena; U, urticaria; V, vomiting.

METHODS

Patients

Thirty-three children, 21 boys and 12 girls (age range, 5 months to 4 years 9 months) with food allergy who had never previously ingested egg or egg-containing foods were selected. According to SPT and RAST results to egg, children were included in either the patient or the control group.

The patient group consisted of 21 children, 13 boys and eight girls (age range, 5 months to 3 years 9 months) with positive SPT reaction and/or specific IgE to egg. Infants were exclusively breast-fed for a period from 2 weeks to 6 months. In 12 infants the onset of the food-related symptoms took place while they were taking only breast milk and while mothers were taking an unrestricted diet. Symptoms caused by food allergens were eczema (19 patients), urticaria (six), angioedema (four), shock (two), hematemesis (one), melena (one), diarrhea (one), and vomiting (one) (Table I). Intolerance to cow's milk was present in 15 patients; to wheat in

six; and to tomato, potato, citrus, rice, pork, and cod in one each. In one exclusively breast-fed infant (patient 8) egg was suspected to have provoked symptoms, because these symptoms appeared when the mother had ingested egg.

The control group included 12 patients, eight boys and four girls (age range, 11 months to 4 years 9 months), with negative SPT and RAST reactions to egg. Symptoms caused by food allergens were eczema (nine patients), urticaria (three), shock (two), angioedema (one), vomiting (one), and diarrhea (one). Intolerance to cow's milk was present in 11 patients; to tomato in 2; and to spinach, soy, wheat, and potato in one each.

All infants attended our clinic because of allergic symptoms appearing before 8 months of age and were monitored every 3 to 6 months. If allergic symptoms were present, the challenge for egg was not performed. At each visit a careful feeding history was obtained from parents or caregivers, who were advised to give an egg-free diet. The week before the challenge, patients

were skin tested and a blood sample was obtained for RAST. If previous results were confirmed, patients were included in the study and the food challenges were conducted.

Skin prick tests

SPT were performed with a 1:20 (wt/vol) concentration of food extract (Bayropharm, Milan, Italy). The size of the skin test wheal was compared with that elicited by 1 mg/ml histamine and by the diluent.

SPT were considered positive if the diameter of the wheal was greater than 3 mm after the diameter of the wheal elicited by the diluent was subtracted and was graded in comparison with the histamine wheal as follows: ++++ if wheal was greater than twice the area of histamine standard, +++ if it was twice the area of histamine standard, ++ if it was equal to the area of the histamine standard, and + if it was half the area of the histamine standard.¹⁴

IgE

Specific IgE antibodies were measured by Phadebas RAST (Pharmacia, Uppsala, Sweden) and graded from 0 to 4 in accordance with the manufacturer's recommendations.

Challenge procedures

DBPCFCs were performed in the allergy unit of the University of Parma Department of Pediatrics, with equipment immediately available for the control of adverse reactions. No drug, including antihistamines (4 to 10 days before challenge), steroids (3 days), theophylline (24 hours), β_2 -agonists (12 hours), and cromolyn (12 hours), was administered to the patients before the challenge.

Increasing doses of dried egg (Lofarma, Milan, Italy), 0.05 to 20 mg, were given every 20 minutes for 2 hours, followed by one boiled egg, to reach a dose greater than the average daily intake. Soy formula or cow's milk were used as placebo in tolerant children. Foods were hidden with soy formula or cow's milk.

The personnel who gave the food, the parents, and the child were unaware whether placebo or egg was given. Food or placebo was randomly given on different days. Patients were observed for 5 hours. Adverse reactions were considered immediate if they appeared within 5 hours and late if after 5 hours. If the challenge result was positive, children were kept in the hospital for 24 hours. If the challenge result was negative, parents openly gave the children at least one egg at home for 4 days. Parents filled a diary card with a score for clinical symptoms. At the end of the challenge period children were examined to check the onset of adverse reactions.

Statistics

Comparison of the challenge results between the study and control group and the relationship between SPT or RAST, and challenge results, were made by

TABLE II. Results of food challenges

Group	No. of challenges	No. (%) of + challenges	+ RAST/ + challenges	+ SPT/ + challenges
Patients	21	13 (61)	12/13	13/13
Controls	12	1 (8)	0/1	0/1
<i>p</i>		<0.01		

+, Positive.

means of a chi-square test. Sensitivity, specificity, efficacy, and negative and positive predictive accuracy¹⁵ for SPT and RAST, alone or in combination, were determined in comparison with the results of DBPCFC. McNemar's test with the use of Yates correction factor for continuity was used for the estimation of differences between SPT and RAST and between SPT, and both SPT and RAST, in predicting clinical hypersensitivity to foods.

RESULTS

Food challenges

Symptoms were evoked in 13 of the 21 children (61%) who underwent challenge with egg in the patient group, and in one of the 12 (8%) in the control group ($p < 0.01$) (Table II). No positive response to placebo was found. Table III shows the egg doses eliciting reactions.

Immediate symptoms

The onset of the manifestations was immediate in 13 of the 14 children (93%) with positive challenges (Table III). In all cases symptoms occurred within 20 minutes from the ingestion of the food. The skin was the most frequently involved organ (12/13 cases [92%]). Positive challenges elicited only cutaneous symptoms in seven of 13 cases (53%). Skin manifestations were pruritus (10 cases), rash (eight), urticaria (five), and angioedema (two). One child had pruritus and swelling of oral mucosa. In three patients vomiting developed. One patient had respiratory manifestations, presenting as a cough. Rhinitis occurred in two patients. Other manifestations recorded were irritability (one patient), drowsiness (one), and anaphylactic shock (one). In 76% of the positive challenge results immediate symptoms developed that the children never had before. Immediate reactions induced by other foods were observed among 46% of the positive challenge results.

Late symptoms

Late symptoms occurred in two of the 14 children (14%) with positive challenge results. In one

TABLE III. Clinical manifestations elicited by egg challenge tests and oral challenge test dose

Group	Case no.	Oral challenge dose	Symptoms	
			Immediate	Late
Patients	2	20 mg	P, R	
	3	5 mg	P/Sw of oral mucosa	
	4	1 egg	U, A	Eczema
	6	20 mg	P, R, V, I, D	
	8	1 egg	P, R, Rn, V	
	10	1 egg	S, U, A	
	11	5 mg	R	
	12	0.5 mg	R, P	
	15	1 egg	P, U	
	16	1 egg	P, U, Rn	
	17	20 mg	P, R	
	18	3 eggs		Eczema
	19	1 egg	P, U, R, V, C	
Controls	5	20 mg	P, R	

A, Angioedema; C, cough; D, drowsiness; I, irritability; P, pruritus; R, rash; Rn, rhinitis; S, shock; Sw, swelling; U, urticaria; V, vomiting.

TABLE IV. Relationship of SPT and RAST with oral challenges

	Oral challenge result		p
	+	-	
SPT			
+	13	8	<0.01
-	1	11	
Total	14	19	
RAST			
+	12	6	<0.01
-	2	13	
Total	14	19	

of the two patients urticaria and angioedema developed immediately after the ingestion of one egg and eczema developed after 24 hours. In the other patient eczema, the only manifestation of allergy, developed after the ingestion of one egg per day for 3 days (Table IV).

Immunologic tests

In the patient group SPT reactions to egg were positive in 20 of 21 cases (95%). SPT reactions to egg were positive in 13 of 14 children (92%) with

TABLE V. Sensitivity, specificity, and predictive indexes of SPT and RAST

	SPT	RAST	SPT and RAST
Sensitivity	0.92	0.85	0.92
Specificity	0.57	0.68	0.57
Predictive value			
Positive	0.61	0.66	0.61
Negative	0.91	0.86	0.91

positive challenges and in eight of 19 subjects (42%) with negative challenge results ($p < 0.01$).

Eighteen of 21 cases (85%) were positive for egg-specific IgE antibodies. RAST reactions to egg were positive in 12 of 14 children (85%) with positive challenge results and in six of 19 subjects (31%) with negative challenge results ($p < 0.01$) (Table IV).

Table V shows the sensitivity, specificity, and positive and negative predictive accuracy calculated for SPT and RAST. Sensitivity and negative predictive value gave the best results, whereas positive predictive value and specificity were poor. There was no significant difference between results of SPT and RAST, or SPTs plus RASTs, in predicting correctly challenge results. To reduce the frequency of the false-positive rate,¹⁶ a RAST score of ++ or more was considered as positive. The predictive accuracy of the RAST results did not change.

DISCUSSION

The results of this study show that among infants with food allergy, clinical hypersensitivity reactions are more likely to develop in those with a positive SPT and/or RAST reaction to egg on the first exposure to the food, compared with subjects with negative test results (61% vs 7%, $p < 0.01$).

Conflicting data have been reported on the usefulness of SPT and RAST results in predicting the development of clinical reaction on the first known administration of specific foods to children at high risk for atopic diseases.

In 24 of 26 infants with positive SPT results for egg at 6 months of age, clinical reactions to egg or other allergens developed before 18 months of age.⁶ A positive RAST reaction to egg was reported to predict the development of allergic symptoms to egg.^{17,18} On the contrary, Lilja and Oman¹⁸ did not find that positive SPT reactions to food preceded the development of atopic diseases in infants with family histories of respiratory atopy. However, in these studies it was not documented

whether reactions occurred on the first exposure; the characteristics of the patients were different from those in the present report, making a comparison with our results unsuitable. Moreover, such studies were likely to be highly subjective because the diagnosis of food allergy was based simply on the clinical history. This has been found to be unreliable¹⁹⁻²² compared with provocation challenge.

We found that in infants with food allergy, a positive SPT reaction to egg was associated with a higher incidence of positive challenges in comparison with subjects who had negative SPT results ($p < 0.01$). Positive challenge results occurred in infants with positive RAST reactions to egg more frequently than in infants who had negative RAST results ($p < 0.01$). This suggests that the clinical symptoms induced by the challenge were IgE mediated.

Because we had carefully checked that infants had never had egg before challenge, sensitization must have occurred either in utero^{11, 23-26} or more commonly after birth, through breast milk.^{7, 27-29}

Our findings show that the administration of a challenge in graded amounts is advisable because symptoms are dose dependent,³⁰ although new serious immediate hypersensitivity reactions are not avoided.³¹ Therefore appropriate emergency equipment and personnel should be available.

Immediate reactions (93%) were more common than late symptoms. It seems reasonable to suspect that the latter were probably caused by a late-phase allergic reaction (case 4)³² and to ingestions of large quantities of egg (case 18).³⁰

In clinical practice offending foods may be suspected on the basis of SPT and RAST results.^{31, 33-36} The present study confirms previous reports of poor SPT and RAST specificity, and positive predictive accuracy,^{34, 35} and of excellent negative predictive accuracy.^{20, 34}

Furthermore, our data show that SPT and RAST sensitivity highly agree with the findings of Bock et al.²⁰ but not with those of Sampson and Albergo.³⁴ Only children with atopic dermatitis were examined in this latter study.

The pattern of the data suggests that a negative SPT and RAST reaction to egg should be considered useful to rule out clinical hypersensitivity reactions on the first exposure. Moreover, a positive SPT or RAST result could be used for a screening of sensitization. However, further analysis by controlled food challenges are warranted because of the high false-positive rate.

In previous studies^{34, 35} the diagnostic accuracy

of SPT and RAST, compared with DBPCFC, was similar. SPT and RAST results were concordant in 73% of the patients with atopic dermatitis³⁴ and in 93% of those with fish allergy.³⁷ In this study RAST or the combination of SPT and RAST did not provide advantages over SPT alone in identifying infants who will have had reactions on the first known administration of egg. Therefore RAST should be reserved for those patients in which SPT cannot be performed.³⁴ In conclusion, these results show that in infants with food allergy a significant correlation between the results of SPT to egg and clinical hypersensitivity reactions on the first exposure to the food is present. Therefore SPT with egg may be useful to predict egg allergy before the introduction of that food into the diet.

REFERENCES

1. Fergusson DM, Horwood LJ, Beautrais AL, Shannon FT. Eczema and infant diet. *Clin Allergy* 1981;11:325-31.
2. Hill DJ, Hosking CS. The Melbourne milk allergy study, 1976 to 1988. In: Hamburger RN, ed. Food intolerance in infancy: allergology, immunology and gastroenterology. New York: Raven Press, 1989:203-22.
3. Arshad SH, Matthews S, Gant C, Hide DW. Effect of allergen avoidance on development of allergic disorders in infancy. *Lancet* 1992;339:1493-7.
4. Kajosaari M, Saarinen UM. Prophylaxis of atopic disease by six months' solid food elimination. *Acta Paediatr Scand* 1983;72:411-4.
5. Zeiger RS, Heller S, Mellon MH, O'Connor RD, Hamburger RN. Effectiveness of dietary manipulation in the prevention of food allergy in infants. *J ALLERGY CLIN IMMUNOL* 1986;78:224-38.
6. Kjellman NIM, Björkstén B, Hattévig G, Falth-Magnusson K. Natural history of food allergy. *Ann Allergy* 1988;61: 83-7.
7. Cant A, Marsden RA, Kilshaw PJ. Egg and cows' milk hypersensitivity in exclusively breast fed infants with eczema, and detection of egg protein in breast milk. *Br Med J* 1985;291:932-5.
8. Warner JO. Food allergy in fully breast-fed infants. *Clin Allergy* 1980;10:133-5.
9. Hamburger RN, Heller S, Mellon MH, O'Connor RD, Zeiger RS. Current status of the clinical and immunological consequences of a prototype allergic disease prevention program. *Ann Allergy* 1983;51:281-90.
10. Hattévig G, Kjellman B, Björkstén B. Clinical symptoms and IgE responses to common food proteins in atopic and healthy children. *Clin Allergy* 1984;14:551-9.
11. Businco L, Marchetti F, Pellegrini G, Perlini R. Predictive value of cord blood IgE levels in "at-risk" newborn babies and influence of type of feeding. *Clin Allergy* 1983;13:503-8.
12. van Asperen PP, Kemp AS, Mellis CM. Immediate food hypersensitivity reactions on the first known exposure to the food. *Arch Dis Child* 1983;58:253-6.
13. Lilja G, Dannaeus A, Foucard T, Graff-Lonnevig V, Johansson SGO, Ohman K. Effect of maternal diet during late pregnancy on the development of atopic diseases in infants

- up to 18 months of age: in vivo results. *Clin Exp Allergy* 1989;19:473-9.
14. Businco L, Baldini G, Galli E, et al. Interpretazione delle indagini immuno-allergologiche per la diagnosi delle allergopatie respiratorie infantili da inalanti. *Riv Immunol Allergol Pediatr* 1989;2:37-49.
 15. Galen RS, Gambino SR. Beyond normality: the predictive value and efficiency of medical diagnoses. New York: John Wiley & Sons, 1975.
 16. DeFilippi I, Yman L, Schroeder H. Clinical accuracy of updated version of the Phadebas RAST test. *Ann Allergy* 1981;46:249-51.
 17. Dannaeus A, Johansson SGO, Foucard T. Clinical and immunological aspects of food allergy in childhood. II. Development of allergic symptoms and humoral immune response to foods in infants of atopic mothers during the first 24 months of life. *Acta Paediatr Scand* 1978;67:497-504.
 18. Lilja G, Oman H. Prediction of atopic disease in infancy by determination of immunological parameters: IgE, IgE- and IgG-antibodies to food allergens, skin prick tests and T-lymphocyte subsets. *Pediatr Allergy Immunol* 1991;2:6-13.
 19. May CD. Objective clinical and laboratory studies of immediate hypersensitivity reactions to foods in asthmatic children. *J ALLERGY CLIN IMMUNOL* 1976;58:500-16.
 20. Bock SA, Lee WY, Remigio LK, May CD. Studies of hypersensitivity reactions to foods in infants and children. *J ALLERGY CLIN IMMUNOL* 1978;62:327-34.
 21. Bock SA, Atkins FM. Patterns of food hypersensitivity during sixteen years of double-blind placebo-controlled food challenges. *J Pediatr* 1990;117:561-7.
 22. Bock SA, Sampson HA, Atkins F et al. Double-blind placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J ALLERGY CLIN IMMUNOL* 1988;82:986-97.
 23. Zeiger RS. Atopy in infancy and early childhood: natural history and role of skin testing [Editorial]. *J ALLERGY CLIN IMMUNOL* 1985;75:633-9.
 24. Bjorksten B, Kjellman NIM. Perinatal factors influencing the development of allergy. *Clin Rev Allergy* 1987;5:339-47.
 25. Miller DL, Hirvonen T, Gitlin T. Synthesis of IgE by the human conceptus. *J ALLERGY CLIN IMMUNOL* 1973;52:182-8.
 26. Michel FB, Bousquet L, Greiller P, Robinet-Levy M, Coulomb Y. Comparison of cord blood immunoglobulin E and maternal allergy for the prediction of atopic disease. *J ALLERGY CLIN IMMUNOL* 1980;64:422-30.
 27. Cavagni G, Paganelli R, Caffarelli C, et al. Passage of food antigens into circulation of breast-fed infants with atopic dermatitis. *Ann Allergy* 1988;61:361-5.
 28. Axelsson J, Jakobsson I, Lindberg T, Benediktsson B. Bovine β -lactoglobulin in the human milk: a longitudinal study during the whole lactation period. *Acta Paediatr Scand* 1986;75:702-7.
 29. Machtinger S, Moss R. Cow's milk allergy in breast-fed infants: the role of allergen and maternal secretory IgA antibody. *J ALLERGY CLIN IMMUNOL* 1986;77:341-4.
 30. Hill DJ, Duke AQM, Hosking CS, Hudson I. Clinical manifestations of cows' milk allergy in childhood. II. The diagnostic value of skin test and RAST. *Clin Allergy* 1988;18:481-90.
 31. Bahna SL. Practical considerations in food challenge testing. *Immunol Allergy Clin North Am* 1991;11:843-50.
 32. Dolovich J, Hargreave FE, Chalmers R, et al. Late cutaneous allergic responses in isolated IgE-dependent reaction. *J ALLERGY CLIN IMMUNOL* 1973;52:38-45.
 33. Sampson HA, McCaskill C. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatr* 1985;107:669-75.
 34. Sampson HA, Albergo R. Comparison of results of skin tests, RAST and double-blind placebo-controlled food challenges in children with atopic dermatitis. *J ALLERGY CLIN IMMUNOL* 1984;74:26-33.
 35. Bahna SL, Gandhi MD. Reliability of skin testing and RAST in food allergy diagnosis. In: Chandra RK, ed. Food allergy. St John's, Newfoundland, Canada: Nutrition Research Foundation, 1987:139-47.
 36. Atherton DJ, Sewell M, Soothill J, Wells RS. Double-blind crossover trial of antigen avoidance diet in atopic eczema. *Lancet* 1978;1:401-3.
 37. Aas K. The diagnosis of hypersensitivity to ingested foods: reliability of skin testing and the radioallergosorbent test with different materials. *Allergy* 1978;8:39-50.