

Egg allergy in infancy predicts respiratory allergic disease by 4 years of age

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Sensitization to hen's egg early in life has been proposed as a predictor for respiratory allergic disease during childhood. However, symptomatic egg allergy in infancy has not been studied in this context. In 1989, a cohort of consecutive births was recruited. Data on family history of atopy and environmental factors were collected. At 4 years of age, 1218 children were seen of whom 981 were skin-prick tested with a range of food and aero-allergens. Of the 1218 children, 29 (2.4%) had suffered symptomatic egg allergy (20 during infancy). Egg allergy in infancy was associated with increased respiratory (asthma, rhinitis) allergic disease (odds ratio [OR] 5.0, 95% confidence intervals [CI] 1.1–22.3; $p < 0.05$) at 4 years of age, with a positive predictive value (PPV) of 55.0%. The addition of infantile eczema to egg allergy increased the PPV to 80% whereas the addition of family history of atopy had no effect. Egg allergy also increased aero-allergen sensitization (OR 6.1, CI 1.1–37.5; PPV 61.1%; $p < 0.05$). As a predictor for respiratory allergic disease and aero-allergen sensitization, it carried a high specificity but poor sensitivity. Hence, egg allergy in infancy, especially when coexisting with eczema, increases respiratory allergic symptoms and aero-allergen sensitization in early childhood.

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Hen's egg is a common food and is usually introduced early in life, often within the first 6 months. During infancy, sensitization predominantly occurs to foods such as egg and cow's milk. The link between egg allergy and infantile eczema is well-established. The first suggestion for an etiological role of egg allergy in infantile eczema was made 80 years ago through the observation that elimination of egg and milk from the diet often led to improvement in symptomatology (1). Subsequent studies went a step further by demonstrating a relapse of eczema following reintroduction of egg (2). More recently, randomized controlled studies of food allergen avoidance for a period of time after birth have demonstrated a reduction in the prevalence of infantile eczema (3, 4). One randomized, controlled study of children with eczema and sensitivity to egg showed significant improvement in the extent and severity of eczema after a period of egg exclusion (5). The maximum benefit was seen in those who had extensive eczema at baseline.

Fortunately, egg allergy in infancy and early childhood occurs as a transitory phenomenon (6).

Studies of children genetically predisposed to atopy show that sensitization to egg in infancy increases the risk of respiratory allergic disease during childhood (7, 8). In a recent publication, Burr et al. followed a birth cohort of high-risk children and reported that egg sensitivity in infancy was strongly associated with eczema, asthma, and house dust mite sensitivity in these children at the age of 7 years (8). The authors postulated that avoidance of egg in infancy may reduce the subsequent development of asthma and aero-allergen sensitization. However, studies of food allergen avoidance in infancy have been uniformly unsuccessful in preventing respiratory allergic disease (3, 4). Previous reports have confirmed the association between egg sensitization and respiratory allergy (7, 8). However, symptomatic egg allergy in infancy and the subsequent development of aero-allergen sensitization and respiratory allergic disease has not been studied.

This prospective whole-population birth-cohort study correlates infantile egg allergy with family history of atopy and with the

development of respiratory allergic symptoms and aero-allergen sensitization by the age of 4 years.

Subjects and methods

Study population

Of 1536 consecutive births on the Isle of Wight between January 1989 and February 1990, 1456 were available for follow-up (9). The findings at 1, 2, and 4 years have been reported previously (9–11). Details of factors such as maturity, birth weight, season of birth, number of siblings, family history of atopy, social class, parental smoking, and presence of household pets, were recorded. A total of 1218 children were reviewed at the age of 4 years.

Diagnostic criteria for atopic disease

To maintain consistency, the same diagnostic criteria were employed at each follow-up (9). Asthma required three or more separate episodes of wheeze, each lasting 3 days, in the preceding year; eczema constituted recurrent, scaly, pruritic, erythematous rash in a flexural distribution lasting > 6 weeks; rhinitis required at least two of three nasal symptoms of discharge, blockage, and recurrent sneezing, accompanied by eye symptoms, occurring most days for ≥ 6 weeks. A diagnosis of food allergy was based on a history of skin rash, respiratory or abdominal symptoms within 4 h of ingestion of a particular food, on two separate occasions. Food challenges were not performed but confirmation of sensitization to the offending food was sought in every case by performing a skin-prick test (SPT).

SPTs

Egg extract was included in the standard SPT battery at each follow-up. At 1 and 2 years of age, only those children who had symptoms of allergic disease (asthma, eczema, rhinitis, food allergy) were given SPTs (10, 11). Of the 1218 children reviewed at 4 years of age, 249 had received SPTs at their first birthday. In contrast, at 4 years of age, all the children were offered SPT, within 1 month before or after their birthday, using a standard battery of aero-allergens: house dust mite (*Dermatophagoides pteronyssinus*), grass pollen mix, cat and dog epithelia, *Alternaria alternata*, and *Cladosporium herbarum*; and food allergens: milk, egg, soya, cod, wheat, and peanut. Eventually, 981 of the 1218 children seen at 4 years of age had received a SPT (9). Histamine (0.1%) in phosphate-buffered saline

(PBS), and physiological saline were used as positive and negative controls, respectively. All extracts were obtained from Biodiagnostics (Biodiagnostic, Reinbeck, Germany). A mean wheal diameter at least 3 mm greater than the negative control at 15 min was judged as positive. Peanut and tree nut sensitization was studied separately and has been reported previously (12).

Statistical analysis

Data was entered into a computer file (SPSS PC+, V4; SPSS Inc., Chicago, USA). Associations between categorical variables were studied by using the chi-square test with Yate's correction. For contingency tables with fewer than 10 patients in any cell, the Fisher's Exact test was applied. Specificity, sensitivity, and positive predictive value (PPV) were calculated by using the method described by Galen & Gambino (13). Multivariate logistic regression was used to assess independent effects of various risk factors for atopy, and adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated. For logistic regression analysis, the control values of different variables included: no family history of atopy; female gender; birth weight ≥ 2.5 kg; winter birth; cord serum immunoglobulin E (IgE) < 0.5 kμ/l; formula feeding after 3 months of age; higher socio-economic group (social class 1, 2, or 3 according to the Registrar General's classification); no maternal smoking; no pets in the house; and an absence of eczema, egg, and cow's milk allergy during infancy.

Informed parental consent was obtained before the birth of each child and at each subsequent follow-up. The study was approved by the Local Research Ethics Committee.

Results

Of the 1218 children reviewed at 4 years of age, 29 (2.4%) had suffered symptoms of allergy to egg by the age of 2 years, with 20 developing it during infancy. No new cases of egg allergy were diagnosed after the second birthday and, by 4 years of age, 21 of the 29 with early life egg allergy had 'grown out of it'. Rash (facial or generalized) and flare of eczema constituted the main symptoms of egg allergy (21 of 29 patients), followed by gastro-intestinal symptoms (vomiting, colic, diarrhea; 17 patients). Wheeze following ingestion of egg was reported in two children only.

At 4 years of age, respiratory allergic disorders were noted to be more common than eczema or food allergy (9). Egg allergy during infancy was more common among those with a positive

family history of atopy: 17 of 713 (2.4%) vs. three of 505 (0.6%), $p < 0.05$. Allergy to egg, whether cumulative or during infancy, correlated significantly with respiratory allergic symptoms (asthma and/or rhinitis) at 4 years of age (Table 1). In contrast, allergy to cow's milk did not significantly increase the incidence of asthma: 12 of 54 with milk allergy (22.2%) vs. 169 of 1164 (14.5%) without milk allergy, NS, by 4 years of age. The impact of allergy to foods other than milk and egg could not be assessed because it was reported in only a few infants: wheat in six, cod in two, and peanut in one. Approximately 50% of babies and toddlers showing manifestations of egg allergy developed asthma and/or rhinitis (16 of 29, $p < 0.001$) by 4 years of age. One-hundred and ninety of the 981 children who received an SPT at 4 years of age had reacted positively to one or more aero-allergens. Early-life egg allergy increased the likelihood of SPT reactivity to common aero-allergens (Table 2). There was a significant association between egg allergy and the subsequent development of sensitization to a number of individual aero-allergens, including house-dust mite, grass pollen, cat, and dog (Table 2). Household exposure to pet cat (20.7 vs. 37.3%) or dog (13.8 vs. 29.3%) seemed lower among children with early-life egg allergy but the difference did not reach statistical significance. Owing to only a small number of cases of egg allergy in infancy, its sensitivity for respiratory allergic disease and aero-allergen sensitization by 4 years of age was poor (5.4% and 6%), despite having a high specificity (99% and 99.1%, respectively). The PPV of egg allergy for asthma (40%) or rhinitis (20%) at 4 years of age was low. When asthma and rhinitis were taken together (any respiratory allergic disease), its PPV increased to 55%. The PPV of egg allergy for aero-allergen sensitization (61%) was marginally better than that for respiratory allergic symptoms at 4 years of age. Ten infants had egg allergy as well as eczema. Eight of these infants subsequently developed respiratory allergic mani-

festations as compared to 168 of 1086 (15.5%) who had neither egg allergy nor eczema ($p < 0.001$; PPV: 80%). In contrast, combining a family history of atopy and egg allergy did not enhance the PPV (57.1%) for respiratory allergic disease.

Two hundred and forty-nine children were given a SPT to egg at 1 year of age, of whom 29 (11.6%) reacted positively. Of these, 13 had suffered symptoms of egg allergy during infancy whereas 16 were tolerant of egg. In addition, seven babies with a history of allergic reactions to egg had a negative SPT to egg on their first birthday. The association of skin test reactivity to egg at 1 year of age with respiratory allergic disease (15 of 29; PPV: 51.7%, $p < 0.01$) and aero-allergen sensitization (19 of 27; PPV: 70.4%, $p < 0.001$) by 4 years of age was similar to that of symptomatic egg allergy. Seven of the 16 children who had a positive SPT but were tolerant of egg (non-clinical egg sensitization) also progressed to develop respiratory allergic disease by 4 years of age. At 1 year of age, a significantly higher level of cat sensitization was observed among those with a positive SPT to egg (33.3% vs. 8.1%, $p < 0.05$).

An independent effect of various risk factors for specific allergic disorders in children at 4 years of age has been reported previously (9). Although allergy to egg (cumulative) was associated with increased aero-allergen sensitization at 4 years of age, its independent association with specific allergic disorders such as asthma or rhinitis could not be established (9). Nevertheless, when asthma and rhinitis were combined (i.e. as any respiratory allergy), egg allergy had a significant independent association (Table 3). A positive family history (maternal history) of atopy, low birth weight (< 2.5 kg), low social class (class 4 or 5 based on the Registrar General's classification), or infantile eczema and egg allergy, each had an independent association with respiratory allergic symptoms in children at 4 years of age. For sensitization to aero-allergens, apart from egg allergy, paternal

Table 1. The relationship of egg allergy to respiratory allergic symptoms in children at 4 years of age

			Egg allergy†	
			In infancy (n=20)	Cumulative (n=29)
Any respiratory allergic symptoms	Yes	(n=218)	11 (5.0)***	16 (7.3)***
	No	(n=1000)	9 (0.9)	13 (1.3)
Asthma	Yes	(n=181)	8 (4.4)**	12 (6.6)***
	No	(n=1037)	12 (1.2)	17 (1.6)
Rhinitis	Yes	(n=65)	4 (6.2)*	7 (0.8)***
	No	(n=1153)	16 (1.4)	22 (1.9)

†Number (%) of patients.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (Fisher's Exact test).

Table 2. The relationship of egg allergy to aero-allergen sensitization in children at 4 years of age

	Reactions to SPT	Egg allergy†	
		In infancy (n=20)	Cumulative (n=29)
Any aero-allergen	+ (n=190)	11 (6)***	16 (8)***
	– (n=791)	7 (1)	11 (1)
House-dust mite (<i>D. pteronyssinus</i>)	+ (n=117)	9 (8)***	13 (11)***
	– (n=864)	9 (1)	14 (2)
Grass pollen	+ (n=77)	4 (5)*	8 (10)***
	– (n=904)	14 (1)	19 (2)
Cat	+ (n=57)	6 (10)***	10 (17)***
	– (n=924)	12 (1)	17 (2)
Dog	+ (n=24)	2 (8)	3 (12)*
	– (n=957)	16 (2)	24 (2)

†Number (%) of patients.

*p < 0.05; ***p < 0.001 (Fisher's Exact Test).

Skin prick test (SPT) responses to *Alternaria* and *Cladosporium* were not related significantly to early-life egg allergy. *D. pteronyssinus*, *Dermatophagoides pteronyssinus*.

atopy, male gender, and elevated cord serum IgE were significant risk factors. Evaluation of sensitivity to individual aero-allergens at 4 years of age revealed a significant association of egg allergy to cat sensitization only (OR: 16.7; CI: 3.3–54.6; p < 0.001).

Discussion

The incidence of egg allergy in infancy and early childhood varies in different populations and figures from 0.3% to 7% have been quoted (14, 15). In our birth cohort, an incidence of 2.4% by 2 years of age was recorded and, as observed by others, symptomatic egg allergy declined after the second birthday (7, 8). The term 'egg intolerance' may be more appropriate for those who had suffered adverse reactions to egg and yet they had a negative SPT response to egg. However, these children satisfied the accepted clinical definition of egg allergy and thus may not have developed skin test responses by 1 year of age. Symptomatic allergy to foods without SPT positivity is not uncommon during infancy (16). Previous reports suggest that 40–80% of egg-allergic children outgrow their allergy by 3–6 years of age (14, 17). However, many children sensitized to egg early in life subsequently develop sensitization to aero-allergens and symptoms of respiratory allergic disorders (7–9).

In 1987, Hattevig et al. reported their results on a small cohort (n=86) followed-up from birth to 7 years of age (7). They found that egg sensitization based on radio-allergosorbent test (RAST) at 1 year of age had high specificity and a moderate level of sensitivity for allergy, both cumulative (98% and 32%) as well as at 7 years of age (97% and 50%). Furthermore, egg sensitization also increased sensitization to inhalant allergens at 7 years of age (96% specificity and

56% sensitivity). Subsequent larger studies (including this study) confirm the high specificity of egg sensitization for respiratory allergic sensitization and symptoms in childhood but they yield much lower sensitivity values (18). The results of Hattevig et al. may be influenced by the small number of subjects in their study, or perhaps by the fact that they excluded males and those with a rhesus-positive blood group (7). The Isle of Wight study included almost all consecutive live births on the island over a period of 14 months and can therefore be taken as a whole-population birth-cohort study. As at 1 and 2 years of age only those who had symptoms of allergic disease were given SPTs, the true prevalence of sensitization to egg in infancy could not be estimated. It is possible that giving SPTs to the whole cohort at 1 year of age would have altered the results. Hence, estimates from

Table 3. Effect of various risk factors on the development of respiratory allergic symptoms and aero-allergen sensitization in children at 4 years of age

Risk factors	Respiratory allergic symptoms	Aero-allergen sensitization
Positive family history of atopy	2.2 (1.3–3.5)***	1.3 (0.9–1.7)
Maternal atopy	1.8 (1.1–3.0)*	1.1 (0.8–1.4)
Paternal atopy	1.1 (0.8–1.4)	1.7 (1.2–3.4)**
Male gender	1.0 (0.8–1.3)	1.7 (1.0–2.8)*
Low birth weight	2.8 (1.0–7.7)*	1.9 (0.8–4.7)
High cord IgE	1.4 (0.9–1.9)	2.5 (1.3–4.8)**
Low social class	2.4 (1.3–3.9)****	1.4 (0.9–1.7)
Egg allergy		
In infancy	5.0 (1.1–22.3)*	6.1 (1.1–37.5)*
Cumulative	5.9 (1.6–22.4)**	4.6 (1.2–17.8)*

Results are presented as adjusted odds ratios (95% confidence intervals) calculated by stepwise logistic regression analysis.

*p < 0.05; **p < 0.01; ***p < 0.005; ****p < 0.001.

Other factors included in the model and found to be non-significant were: formula feeding in the first 3 months of life, maternal smoking, season of birth, exposure to household pets, and allergy to cow's milk.

IgE, immunoglobulin E.

this study of the predictive value of SPT positivity to egg at 1 year of age for subsequent development of respiratory allergy may not be broadly applicable despite the fact that the results are in general agreement with those reported by others for a positive RAST to egg in children at 1 year of age (18).

Provocation tests with egg to confirm egg allergy were not performed. Nonetheless, the results reveal that the predictive capacity of symptomatic egg allergy (based on history alone) is similar to that of sensitization to egg (as assessed by SPT) for the development of respiratory allergic disease and aero-allergen sensitization.

For respiratory allergy we used symptoms, as well as allergic sensitization, as end-points. Not all children with allergic respiratory symptoms are sensitized, and vice versa. Studies have shown that a large minority of asthma in childhood is non-atopic. A recent meta-analysis studied the association between asthma and atopy (defined by elevated total serum IgE or positive SPT to one or more common allergens) (19). Based on weighted mean values, it reported that approximately 42% of asthmatic children do not have evidence of atopy. In the Isle of Wight study, the battery of aero-allergens and food allergens used for SPTs in children at 4 years of age seemed adequate. Hence it is unlikely that atopic asthma was under-estimated (atopic vs. non-atopic: 71 vs. 90) (9).

Certainly, in early childhood, asthmatic symptoms correlate with a number of influences including: low birth weight; method of feeding; passive exposure to tobacco smoke; and inter-current respiratory infections. These results, based on logistic regression analysis, were obtained after the inclusion of environmental factors (except for early-life respiratory infections) together with data on heredity and cord IgE levels (Table 3). Although factors other than atopy may indeed account for respiratory allergic symptoms in children, the results of logistic regression clearly show an independent association of egg allergy in infancy with respiratory allergy (irrespective of being classed as atopic or non-atopic). Premature birth, with or without mechanical ventilation, in the neonatal period was not associated with respiratory allergic symptoms or aero-allergen sensitization. The length of gestation (mean $\pm$ SD) was similar in children who developed respiratory allergic symptoms and sensitization to aero-allergens at 4 years of age and in those who did not (39.8 ± 1.8 vs. 39.9 ± 1.5 weeks, and 40.1 ± 1.3 vs. 39.9 ± 1.6 weeks, respectively; both NS). Furthermore, no child with respiratory symptoms

had been diagnosed as having another lung disorder, such as cystic fibrosis, or a congenital broncho-pulmonary defect.

The German Multicentre Allergy Study (MAS) reported that serum egg-specific IgE > 2 k μ /l at the age of 1 year increased the risk of sensitization to both indoor and outdoor aero-allergens by age 3 years, with sensitivity, specificity, and PPV of 16%, 99%, and 77%, respectively (18). Our study showed a lower sensitivity for both symptomatic egg allergy and egg sensitization, with specificity and PPV similar to the MAS report. This probably reflects a dissociation between sensitization and symptomatic egg allergy.

Early life egg sensitivity has been proposed as a marker for respiratory allergic disease, such as asthma, during childhood (7, 8, 18). However, as only a small number of babies develop allergy to egg, its sensitivity for subsequent respiratory allergy and aero-allergen sensitization remains low. Combining egg allergy with a family history of atopy was rather unrewarding with respect to boosting the sensitivity and PPV. In a previous report, the addition of family history to egg sensitization in children at 1 year of age further reduced the sensitivity without improving the predictive capacity for the development of aero-allergen sensitization (18). Our results were similar, showing identical PPVs of egg allergy with and without a family history of atopy (57.1% and 61.1%, respectively) for the development of aero-allergen sensitization. In contrast, egg allergy and eczema coexisting in infancy, seemed a better predictor for respiratory allergy and aero-allergen sensitization in children at 4 years of age, although the number in this subgroup was small ($n = 10$).

A positive SPT to egg in 6-month-old infants has been linked to persistently high median total IgE levels throughout childhood and to an increased incidence of sensitization to house dust mite in children at 7 years of age (8). However, it is not certain whether early-life egg allergy predisposes to subsequent respiratory allergic manifestations or whether it merely acts as a marker (akin to infantile eczema) during the so-called 'allergic march' among at-risk children.

An association between egg allergy and sensitization to cat has not been reported previously. In our study, this association was observed at both 1- and 4-year follow-up time-points, despite a relatively lower exposure of egg-allergic children to cat at home. Structural similarities between egg albumin and the cat allergens have not been described. It is possible that egg and cat sensitization represent markers for atopy.

Our study shows that the predictive capacity of symptomatic egg allergy in infancy for respiratory symptoms and sensitization to aero-allergens at 4 years of age is similar to that of egg sensitization. It is not a useful screening method owing to a low sensitivity. However, based on a high specificity, infants with egg allergy (irrespective of SPT or RAST positivity) should be regarded as being at a high risk for the development of respiratory allergy.

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