

Parental Eczema Increases the Risk of Double-Blind, Placebo-Controlled Reactions to Milk but Not to Egg, Peanut or Hazelnut

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Key Words

Food hypersensitivity · Immediate hypersensitivity · Food challenges

Abstract

Background: While genetic factors are known to be important in the development of sensitization to foods, it is not known whether they also play a role in clinical allergic reactivity to foods. **Objective:** We aimed to determine whether parental atopic diseases are associated with a higher risk of a reaction to common allergenic foods when tested in a double-blind, placebo-controlled food challenge (DBPCFC). **Methods:** Parents of children suspected of being food allergic were interviewed about their own and their child's atopic history. Specific IgE and skin prick tests to food allergens and the outcome of food challenges in the child were recorded. **Results:** Data from 553 double-blind food challenges performed in 396 children were analyzed. The foods tested were milk (n = 185), egg (n = 110), peanut (n = 198) and hazelnut (n = 60). Only parental eczema was significantly associated with positive outcomes for food challenges with

milk after correction for age, sex, atopic comorbidity in the child and milk-specific IgE test results (odds ratio 3.1, 95% confidence interval 1.5–6.3). **Conclusions:** Children with a positive DBPCFC to milk more frequently have parents with eczema than children with a negative test. This effect of parental eczema was not seen in children challenged with egg, peanut or hazelnut. Clinical reactivity to milk may be caused by genetic factors which are shared with parental eczema to a greater extent than clinical reactivity to other foods.

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Introduction

Food allergy shares a number of features with other atopic disorders such as allergic asthma, allergic rhinitis and atopic eczema. This includes the production of IgE antibodies and a high degree of heritability. In recent years, much information has been generated about genes that may influence the development and expression of atopic diseases, particularly asthma [1]. There are also numerous studies documenting sensitization to foods as

an atopic phenotype related to other atopic phenotypes. By comparison, much less is known about phenotypic associations and possible genes that may affect clinical allergic reactivity to foods in sensitized individuals.

Studies on the heritability of food allergy have been difficult to compare and interpret because of differences in the diagnostic methods used for case finding. Many such studies [2–4] rely on suggestive histories and positive specific IgE (sIgE) tests or skin prick tests to the food in question for diagnosis. This may result in overrepresentation of asymptotically sensitized individuals amongst the cases. Such misdiagnosis may be reduced by using double-blind, placebo-controlled food challenges (DBPCFCs) for case finding.

An important question in food allergy genetics is whether there may be shared, pleiotropic genes operative in both food allergy and other atopic conditions. Familial aggregation of parental atopy and clinical allergic reactivity to food in the child may suggest shared genetic factors underlying these clinical entities. We therefore examined the association of atopic phenotypes in parents with the outcome of DBPCFCs in their children. We hypothesized that atopic disease in the parents is associated with clinical reactivity to foods in the child, and we corrected for possible confounders, most notably sensitization to the food in question in the child.

Patients and Methods

Study Population and Sensitization

Patients were seen between 2001 and 2006 at a tertiary care pediatric allergy outpatient clinic because of suspected food allergy. These children underwent DBPCFCs in the course of routine care. At the time of the challenge, information on parental and personal atopic disorders was obtained by interview by a trained allergy nurse and recorded in an electronic database. Children and their parents were asked whether they had received a doctor's diagnosis of asthma, allergic rhinitis, atopic dermatitis or (parents only) food allergy, or whether any medication relating to these diagnoses were previously or currently used. In the children undergoing DBPCFCs, sensitization to the food in question was determined by an ImmunoCap RAST (Phadia AB, Uppsala, Sweden) sIgE test within 6 months of the DBPCFC. In the clinical setting, sIgE results of >0.35 kU/l were considered positive. Children were considered sensitized to the food in question when they had a positive sIgE test. The medical ethics committee of the University Medical Center Groningen deemed consideration of this study unnecessary.

Food Challenges

Active challenges and placebos were randomly administered on separate days with at least a 2-week interval between the two

test days. For the active challenge, the suspected food was disguised in a food to which the child was tolerant. Adequate blinding of test material was validated by sensory testing in a food laboratory [5]. The challenge doses were administered according to incremental scales for the suspected food as described by Vlieg-Boerstra et al. [6]. The challenge was stopped when objective symptoms occurred or when subjective allergic symptoms occurred twice upon two consecutive administrations of the same dose. Objective symptoms and signs were defined as (angio)edema, urticaria, exacerbation of atopic eczema, rash, vomiting, diarrhea, lip or tongue swelling, rhinoconjunctivitis, stridor, coughing, wheezing, hoarseness, collapse, tachycardia and hypotension. Two days after both challenge sessions, late-onset reactions were recorded by telephone questionnaire. Two days after the second challenge session, the code was broken and the outcome of the DBPCFC was assessed as previously described [6]. We selected challenges for the most frequently tested foods, i.e. cow's milk, hen's eggs, peanut and hazelnut.

Statistics

Logistic regressions were used to compare the risk of a reaction to each food tested between children without parents with atopic diseases and children with 1 or 2 parents with atopic diseases. Parental eczema, asthma, rhinitis and food allergy were analyzed in one regression, in order to see if they influenced each other. In a second analysis, the number of separate atopic diseases in the parents (eczema, asthma, rhinitis and food allergy) was counted, with a maximum score of 8 (both parents having all 4 atopic diseases). We then included this number in a logistic regression to examine the effect of the number of parental atopic diseases on the risk of a positive DBPCFC outcome. All logistic regressions were performed using sIgE level, age, sex and atopic comorbidity in the child (eczema, asthma and rhinitis) as covariates. All statistical analyses were performed using SPSS 16 (SPSS Inc., Chicago, Ill., USA).

Results

Study Population

From a total of 776 food challenges, we excluded the data from food challenges that were incomplete, not double-blind or had an ambiguous result. Thus, a total of 553 food challenges performed in 396 patients were included; 251 of the patients were male and 145 were female. The median age was 5.4 years (range 6 months to 17.8 years). In all, 274 children were tested for 1 food, 92 children for 2 foods, 25 children for 3 foods and 5 children for all 4 foods. Further demographics of the children tested for milk, egg, peanut and hazelnut are shown in table 1. There was a notably high level of atopy in the study population. More than 90% of the children tested had already been diagnosed with an atopic disease other than food allergy, most commonly eczema.

Table 1. Demographic statistics of the study population according to DBPCFC test results for challenges with egg, milk, peanut and hazelnut

	Milk DBPCFC		Egg DBPCFC		Hazelnut DBPCFC		Peanut DBPCFC	
	negative	positive	negative	positive	negative	positive	negative	positive
Number of children	101	84	66	44	35	25	89	109
Age, years								
Median	2.8	2.4	4.9	4.2	7.4	7.3	6.8	7.3
Range	0.5–15.1	0.6–16.5	0.8–16.5	0.8–15.8	2.7–16.7	3.2–17.4	1.8–17.6	2.6–17.8
Males, n	66 (65.3)	51 (60.7)	40 (60.6)	33 (75.0)	24 (68.6)	15 (60.0)	64 (71.9)	66 (60.6)
Atopic comorbidity, n								
Any	86 (85.1)	78 (92.9)	60 (90.9)	42 (95.5)	34 (97.1)	25 (100)	82 (92.1)	107 (98.2)
Eczema	85 (84.2)	75 (89.3)	57 (86.4)	41 (93.2)	32 (91.4)	24 (96.0)	73 (82.0)	100 (91.7)
Asthma	32 (31.7)	37 (44.0)	41 (62.1)	23 (52.3)	22 (62.9)	13 (52.0)	58 (65.2)	74 (67.9)
Rhinitis	20 (19.8)	20 (21.6)	27 (40.9)	13 (29.5)	20 (57.1)	14 (56.0)	40 (44.9)	53 (48.6)
None	12 (11.9)	5 (6.0)	4 (6.1)	1 (2.3)	1 (2.9)	0	6 (6.7)	2 (1.8)
Parental atopy, n								
Any	69 (68.3)^b	76 (90.5)^b	47 (71.2)	33 (75.0)	26 (74.3)	19 (76.0)	63 (70.8)	88 (80.7)
Eczema	44 (43.6)^b	54 (64.3)^b	33 (50.0)	22 (50.0)	17 (48.6)	12 (48.0)	38 (42.7)	54 (49.5)
Asthma	20 (19.8)^b	28 (33.3)^b	21 (31.8)	17 (38.6)	9 (25.7)	7 (28.0)	25 (28.1)	35 (32.1)
Rhinitis	53 (52.5)	52 (61.9)	29 (43.9)	23 (52.3)	18 (51.4)	10 (40.0)	44 (49.4)	67 (61.5)
Food allergy	11 (10.9)^b	20 (23.8)^b	14 (21.2)	9 (20.5)	3 (8.6)	5 (20.0)	15 (16.9)	22 (20.2)
None	26 (25.7)	5 (6.0)	14 (21.2)	8 (18.2)	6 (17.1)	5 (20.0)	14 (15.7)	15 (13.8)
Specific IgE, IU/ml								
Median	0.31^a	7.27^a	1.74	10.4	3.13	7.11	1.37^a	21.8^a
Range	0.30–101	0.30–101	0.30–64.6	0.30–101	0.30–101	0.30–101	0.30–45.9	0.30–101
Number of children with sIgE >0.35 IU/ml	45 (44.6)^b	69 (82.1)^b	26 (39.4) ^b	33 (75.0) ^b	27 (77.1)	23 (92.0)	64 (71.9)^b	105 (96.3)^b

Numbers in parentheses are the percentages of the total number of children who tested positive or negative for the food in question, not including the children for which there were no data for that variable.

^a A significant within-food difference between positive and negative challenge outcomes (independent-samples median test).

^b A significant within-food difference between positive and negative challenge outcomes (Pearson's χ^2 test).

Influence of Parental Atopy

In a total of 262 food challenges, the test was considered positive according to the test protocol. Children with 1 or 2 parents with eczema had an odds ratio (OR) of 3.1 [95% confidence interval (CI) 1.5–6.3; $p < 0.01$] for a reaction to milk when compared to children with no atopic parents, even after correction for age, sex, sIgE test results and atopic comorbidity in the child. As can be seen in table 2, parental asthma, rhinitis and food allergy were either not significantly associated with a positive milk challenge test or did not remain significant after correction for the aforementioned variables.

Parental atopic diseases were not a significant risk factor for reactions to the other foods (peanut, hazelnut and egg).

When studying parental asthma, eczema, rhinitis and food allergy in a single model, only parental eczema re-

mained a significant risk factor for a reaction to milk after correction for the other parental atopic diseases (OR 2.9, 95% CI 1.3–6.3; $p < 0.01$; table 2).

Paternal and Maternal Effects

Paternal and maternal atopy (i.e. having any atopic disease) were significant risk factors only in the case of milk allergy, with little difference between the two (paternal atopy: OR 1.4, 95% CI 1.01–1.9; $p = 0.47$; maternal atopy: OR 1.4, 95% CI 1.1–1.9; $p = 0.02$). Analyzed separately, no single paternal or maternal atopic disease was a significant risk factor for a reaction to milk.

The Effects of More Severe Parental Atopy on the Risk of a Reaction to Milk

One atopic disease in the parents increased the risk of the child reacting to milk during the DBPCFCs. Addi-

Table 2. ORs for the risk of a reaction to milk, egg, peanut or hazelnut in the presence of parental atopic diseases before and after correction for age, sex, sIgE test results and atopic comorbidity in the child

	Atopic diseases in a separate model, before correction		Atopic diseases in a separate model, corrected		Atopic diseases together, corrected	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
<i>Milk</i>						
Eczema	2.4 (1.3–4.3)	<0.01	3.1 (1.5–6.3)	<0.01	2.9 (1.3–6.3)	<0.01
Asthma	2.0 (1.0–3.9)	0.048	1.9 (0.8–4.1)	0.12	1.7 (0.7–4.1)	0.23
Rhinitis	1.5 (0.8–2.7)	0.20	1.6 (0.8–3.3)	0.17	1.6 (0.7–3.4)	0.25
Food allergy	2.3 (1.0–5.1)	0.045	1.8 (0.7–4.7)	0.26	0.8 (0.3–2.5)	0.77
Any atopic disease	5.7 (2.1–15.8)	<0.01	6.2 (2.0–19.5)	<0.01	– ¹	–
<i>Egg</i>						
Eczema	1.0 (0.5–2.3)	0.93	0.7 (0.2–2.0)	0.46	0.7 (0.2–2.4)	0.53
Asthma	1.4 (0.6–3.1)	0.42	1.2 (0.4–3.8)	0.79	1.4 (0.4–5.2)	0.64
Rhinitis	1.3 (0.6–2.9)	0.50	1.6 (0.5–4.7)	0.42	1.8 (0.5–6.0)	0.35
Food allergy	0.9 (0.4–2.4)	0.85	1.3 (0.4–4.9)	0.69	1.1 (0.2–5.5)	0.88
Any atopic disease	1.2 (0.5–3.3)	0.68	0.7 (0.2–2.8)	0.59	– ¹	–
<i>Peanut</i>						
Eczema	1.2 (0.7–2.1)	0.51	1.0 (0.5–2.0)	0.92	1.0 (0.4–2.2)	0.99
Asthma	1.1 (0.6–2.1)	0.70	1.2 (0.5–2.5)	0.72	1.0 (0.4–2.4)	0.99
Rhinitis	1.4 (0.8–2.5)	0.28	1.5 (0.7–3.2)	0.26	1.5 (0.7–3.2)	0.34
Food allergy	1.1 (0.5–2.4)	0.73	1.0 (0.4–2.7)	0.97	0.9 (0.3–2.6)	0.85
Any atopic disease	1.3 (0.6–2.9)	0.51	1.5 (0.5–4.2)	0.44	– ¹	–
<i>Hazelnut</i>						
Eczema	1.0 (0.4–2.7)	0.97	1.0 (0.3–3.1)	0.99	0.9 (0.3–3.2)	0.92
Asthma	1.1 (0.4–3.6)	0.84	1.8 (0.4–7.5)	0.43	2.0 (0.4–10.0)	0.42
Rhinitis	0.6 (0.2–1.8)	0.38	0.5 (0.2–1.8)	0.31	0.4 (0.1–1.4)	0.14
Food allergy	2.5 (0.5–11.9)	0.24	1.8 (0.4–9.1)	0.48	1.8 (0.3–10.2)	0.50
Any atopic disease	0.9 (0.2–3.3)	0.85	0.9 (0.2–3.6)	0.83	– ¹	–

These results include the significant within-food differences found in table 1. Significant p values are shown in bold.

¹ The category ‘any atopic disease’ was not included in the logistic regression with the other atopic diseases because that variable itself consists of the sum of all atopic diseases.

tional atopic diseases increased the risk somewhat, i.e. there was a trend for an increased risk of clinical reactions to milk with an increasing number of parental atopic diseases, but this trend did not reach statistical significance ($p = 0.21$). The different atopic diseases were also weighed by multiplying each parental disease by its separate OR, but this did not alter the results (data not shown).

Influence of Sensitization

Allergic sensitization in the child, defined as a positive sIgE test, was a significant risk factor for a clinical reaction to milk (OR 7.7, 95% CI 3.4–17.3; $p < 0.01$) and peanut (OR 21.4, 95% CI 2.7–171.6; $p < 0.01$) but not for hazelnut ($p = 0.38$) or egg ($p = 0.07$).

Discussion

This study in a pediatric population with suspected food allergy shows that parental eczema is associated with a higher risk of a positive food challenge to milk in the child, but not to egg, peanut or hazelnut. This risk is independent of that associated with increasing sensitization to milk allergens. Children undergoing a DBPCFC with milk and having 1 or 2 parents with eczema had a 3.1-fold greater risk of a reaction to milk during the food challenge than children with parents without atopic disease. This effect remained significant after correction for age, sex, sIgE test results and atopic comorbidity in the child, as well as correction for the other parental atopic diseases.

Eczema in the parents was the atopic disease that conveyed the greatest risk of a reaction to milk, whereas rhinitis and asthma were not significantly associated with positive milk challenges. In the case of parental food allergy, the OR dropped more than 10% when corrected for other parental atopic disease, thus indicating that parental food allergy is not a separate risk factor but is dependent on the presence of one of the other parental atopic diseases. In the case of parental asthma, the reason for the loss of significance could be less power and precision with the use of more factors resulting in more missing cases. This is suggested by the fact that the OR does not change much as more variables are added to the logistic regression. A bigger study sample would be necessary to determine if parental asthma is associated with clinical reactivity to milk.

We were unable to find a statistically significant effect of an increasing number of different atopic diseases in the parents on the risk of a reaction to milk. One atopic disease in either parent was clearly associated with an increased risk of clinical reactivity to milk, but more parental atopic diseases did not significantly increase this risk further. The fact that the extent or severity is of little importance beyond the presence of atopy is consistent with the effects of pleiotropic genetic factors.

An important question which emerges from these data is why milk is different from other foods. This is a surprising finding because clinical reactivity to milk is a less stable phenotype over time than clinical reactivity to other foods. Tolerance development to milk occurs in approximately 87% of the children by 3 years [7], whereas values for egg are reported as 37–66% by 10 years [8], and for peanut, only 21% between 4 and 20 years [9].

Another factor may be that cow's milk proteins are more similar to human proteins than egg, peanut or hazelnut proteins, with regard to both amino acid sequence (e.g. ALA [10]) and tertiary structure (e.g. caseins [11]). However, it is unclear what the clinical significance of this similarity is, because in the example of ALA, the similarity does not prevent this protein from being one of the major allergenic proteins in milk [10].

Because cow's milk is given to children earlier in life and in much greater quantities than egg, peanut or hazelnut, and possibly because milk allergy presents earlier in life, it is conceivable that clinical reactivity to foods other than milk is influenced to a greater extent by environmental factors than clinical reactivity to milk. Children tested for milk in our study were also, on average, younger than children tested for the other foods, but age was not a significant risk factor in and of itself ($p = 0.97$).

Environmental factors may therefore have more time to influence the phenotype of clinical allergic reactivity to egg, peanut and hazelnut than to milk, thus obscuring the association with parental eczema, asthma rhinitis and food allergy.

Our findings regarding the significant correlation between parental atopy and the risk of a reaction to milk and the absence of such a correlation with other foods seem to suggest that milk allergy has a strong familial component which is lacking or obscured in egg, peanut and hazelnut allergy. This seems to contradict observations made by other researchers. For example, a twin study by Sicherer et al. [2] found a significantly higher concordance rate ($\chi^2 = 21.38$, $p < 0.0001$) for peanut allergy among monozygotic pairs of twins ($n = 14$; pairwise concordance 64.3%) than among dizygotic pairs ($n = 44$; pairwise concordance = 6.8%), suggesting a significant genetic influence on peanut allergy. A child in this study was considered peanut allergic if he or she had a convincing history of peanut allergy. Furthermore, a study by Tsai et al. [4] found that maternal peanut allergy was a significant risk factor for peanut allergy in the child (OR 5.1, 95% CI 1.7–15.0; $p = 0.003$). This study included 580 families in which 67% of the included children and 14% of the mothers were peanut allergic. In this study, peanut allergy was diagnosed based on a convincing history (criteria included timing and symptoms) and a positive sIgE test [4]. In our study, all children had a convincing history of food allergy and were then classified as clinically reactive or nonreactive by DBPCFC. The associations in the studies by Sicherer et al. [2] and Tsai et al. [4] described above may therefore be more closely related to sensitization than clinical reactivity. This could also explain why we did not find a difference between maternal and paternal effects. Because we did not study specific parental food allergy, we cannot exclude that specific parental allergies (i.e. peanut allergy) are associated with specific allergies in the child, consistent with specific genetic risk factors related to specific foods as was found by Sicherer et al. [2] and Tsai et al. [4].

We found the degree of sensitization to the food in question as determined by sIgE to be associated with an increased risk of a reaction to foods in DBPCFCs for peanut and milk, as has been described by others [12–15]. The first exception in this regard was sIgE for hazelnut. This may have been caused by the fact that the sIgE test used for hazelnut also detects birch pollen sIgE [16]. Secondly, sIgE for egg was also not significant, probably due to limited power caused by missing egg sIgE data in 40 of the 110 cases. By contrast, we only had 5 missing sIgE val-

ues amongst children tested with peanut and no missing values in children challenged with cow's milk.

It has already been established that parental atopy is associated with an increased risk of sensitization to foods [3]. However, our data show for the first time that, in the case of milk, there is an effect of parental eczema on clinical allergic reactivity which is distinct from the effect of sensitization. These findings could be useful in the clinical setting for estimating the chance of a child being reactive to milk when DBPCFCs are undesirable or unavailable. Thus, both the degree of sensitization and the presence of parental eczema may be useful for determining the role of milk ingestion in the occurrence of symptoms.

Familial aggregation of parental eczema (and possibly asthma) with clinical reactivity to milk may suggest shared genetic factors relating to these atopic diseases. These shared genetic factors may be the results of pleiotropic gene(s) that cause both conditions. One such pleiotropic gene may be the filaggrin gene (*FLG*). Loss-of-function *FLG* variants have been found to be associated with eczema and allergic airway disease [17]. In addition, it has been hypothesized that food sensitization and the development of food allergy may occur through more permeable eczematous skin, especially in individuals with *FLG* defects [18]. Recently, loss-of-function *FLG* variants were found to be associated with peanut allergy [19]. However, earlier studies did not find an association between *FLG* mutations and food sensitization to milk, egg, soy or wheat [20, 21]. This may indicate that there are dif-

ferences in the pathogenesis of clinical reactivity to food versus sensitization to food, which may also vary between different types of food allergens. Furthermore, since the effect of parental eczema on clinical reactivity to milk was seen in our study even after correction for eczema in the child, the effects of *FLG* variants may be more complex than a simple association with eczema. Future studies should investigate the role of genes such as *FLG*, which are important in eczema and other atopic diseases, in clinical reactivity to milk.

In summary, our findings show that in contrast to egg, peanut and hazelnut, the risk of clinical reactivity to milk as ascertained by a double-blind food challenge is increased in children of parents who have eczema. Eczema was the only significant parental atopic risk factor after correction for other parental atopic diseases in a logistic regression model. The effect of parental eczema remained significant after correction for age, sIgE tests and atopic diseases in the children themselves. Although atopic genetic factors are associated with sensitization to foods, our data suggest that separate, shared, atopic genetic factors are associated with allergic clinical reactivity to milk.

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