

Original article

Food allergy and food sensitization in early childhood: results from the DARC cohort

Background: The prevalence of food hypersensitivity (FHS) and the relationship with atopic dermatitis (AD) is controversial. The aim of this study was to determine the development of FHS and to correlate this with AD in relation to sensitization and symptoms.

Methods: This study combines new data from birth to 18 months of age with previous published results from 3 and 6 years. The Danish Allergy Research Centre cohort, including 562 children, is a unique, population-based, prospective birth cohort, with clinical examinations at all follow-ups. All children were examined for the development of AD using Hanifin-Rajka criteria and for FHS using interviews, skin prick test (SPT), specific immunoglobulin E (IgE), and food challenge according to EAACI guidelines.

Results: Twenty children were confirmed with FHS to milk, egg, and peanut. FHS peaked at 18 months (3.6%) and then decreased to 1.2% at 72 months of age. No new cases were found after 3 years. Self-reporting could only be confirmed in 31% of cases. Among the 122 children with AD, 18 had FHS (14.8%). FHS was IgE-mediated in 95% of the cases but 16 of 20 children were additionally sensitized to other foods which they tolerated. Children with AD were neither more IgE-sensitized nor had higher levels of IgE when compared with healthy children but they were more persistently sensitized.

Conclusions: Sensitization to foods in young children without food allergy seems to be a normal phenomenon. The discrepancy between sensitization, self-reported food-related symptoms and confirmed FHS illustrates the need to perform standardized oral challenges in order to confirm the diagnosis of FHS.

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Longitudinal prospective studies of adverse reaction to food or food hypersensitivity (FHS) (1) are few and often based on self-reported data (2). Only 30% of self-reported FHS have been confirmed by oral challenge (3–5), which is recommended as the gold-standard for diagnosis of FHS (6). It is generally accepted that children may outgrow their FHS but so far only few challenge-confirmed prospective studies have addressed this (4, 7). Furthermore, the relationship between atopic dermatitis (AD) and FHS is controversial. Among selected children with AD, about one-third have a positive oral challenge to at least one type of food (4, 8–10).

The aim of this study was to determine the development of FHS documented by oral challenges longitudinally from birth to 6 years; to correlate FHS with AD and to describe the relevance of sensitization to food allergens in relation to clinical symptoms. We combined previous published data from 36 (11) and 72 months follow-ups (12) with new unpublished data from birth to 18 months of age.

Materials and methods

Study design

The Danish Allergy Research Centre (DARC) cohort is a unique, population-based, non-interventional, single-center birth cohort of 562 children, born at Odense University Hospital, Denmark (Table 1). They were recruited from a random sample of all children ($n = 1095$) born within the first 14 days of each month from November 1998 to November 1999. Parents declined participation in 435 cases, mainly because of the comprehensiveness of the study and further 98 children were excluded by investigators due to insufficient parental knowledge of Danish, plans to move or serious illness (11–13).

At birth, every child underwent a clinical examination, skin prick test (SPT), cord blood sampling, and an interview was conducted with the child's parents covering atopic predisposition, environmental, and social factors. Follow-up were performed at 3, 6, 9, 12, 18, 36, and 72 months of age. All follow-ups included an interview, clinical examination, SPT, and blood sampling for immunoglobulin E (IgE), except the 9-month follow-up, which only included interview and clinical examination. Parents who did not participate in a

Table 1. Characterization of recruited children

<i>n</i> = 562			
Sex – Male (%)		285	(50.7%)
First born (%)		263	(46.8%)
Complete breast fed ≥ 3 months (%) (<i>n</i> = 524)		336	(64.1%)
Maternal tobacco smoke during pregnancy (%)		183	(32.6%)
Parental medium/high social class* (<i>n</i> = 472)		266	(56.3%)
Mean birth weight (g) [range]		3541	[2100–5000]
Mother's mean age (year) [range]		28.9	[17–42]
Father's mean age (year) [range]		31.0	[19–55]
	Both parents	Only mother	Only father
Parents with Danish origin (%)†	429 (76.6%)	65 (11.6%)	10 (1.8%)
Parents with doctor diagnosed allergy‡ (%)	62 (11.0%)	138 (24.6%)	102 (18.1%)
Parents with doctor diagnosed FHS (%)	2 (0.4%)	22 (3.9%)	11 (2.0%)

FHS, food hypersensitivity.

*Social class I–III according to (34). Social classes for 90 families could not be established, as they at the time of recruitment either were full time students or had never been employed or due to missing data.

†Fifty-five children (9.8%) had neither Danish mother nor father. The cohort included three sets of twins.

‡Atopic dermatitis, allergic rhinitis, food hypersensitivity and asthma.

follow-up were offered a telephone interview by a physician. Response rate at 12, 36, and 72 months follow-ups were 83.3%, 73.1%, and 71.9% respectively. Five hundred thirty-four children (95.0%) underwent a clinical examination at least once during the 6 years.

Lost participants were addressed three times during the first 6 years. At birth, data on weight, apgar score, and parental allergic disposition from the included 562 children did not differ from the 435 children who refused participation. At 12 months, prevalence in AD was not different in children lost during the first year, i.e., the 435 non-participating as well as drop-outs were compared with participating children (13). Kjaer et al. (12) also found no difference, comparing characteristics of children recruited and those investigated at 6 years follow-up.

Skin prick test

Skin prick test was performed as skin 'prick-prick' technique on the volar surface of the forearms with a 1-mm lancet (ALK-ABELLÓ, Hørsholm, Denmark) according to EAACI guidelines (14, 15). A positive SPT was defined as a mean wheal size ≥ 3 mm larger than the negative control. From 0 to 18 months of age, SPT was made with commercially available cow's milk and hen's egg extracts (ALK-ABELLÓ) and fresh cow's milk. Allergic activity of extract varies, whereas fresh food usually results in better sensitivity and reproducibility (16). Therefore at 36 and 72 months follow-up, fresh Brazil nut, codfish, cow's milk, hazelnut, hen's egg, peanut, shrimp, celery root, and wheat was used for SPT. Furthermore, fresh soy was tested at 72 months.

Total and specific IgE

Total and specific IgE (s-IgE) were analyzed between 0 and 36 months of age by Magic Lite (ML) (ALK-ABELLÓ) and at 72 months by ImmunoCap (CAP) (Phadia, Uppsala, Sweden). The shift was prompted by logistical reasons, however, a high comparability between ML and CAP has previously been demonstrated (17). At 0–18 months, s-IgE to codfish, cow's milk, hen's egg, peanut, and wheat was tested; at 36 months soy and shrimp were added and at 72 months of age, hazelnut, Brazil nut, and celery root were additionally included. Tests were performed

in accordance with the manufacturer's instructions and classified as a positive test result when s-IgE $\geq$ class 1 (ML > 1.43 SU/ml; CAP > 0.35 kU/l).

Diagnostic procedure

Children were diagnosed with suspected FHS (i.e., possible FHS), either when parents reported any adverse reactions to foods in the interview or when a child had a positive outcome in at least one of the follow-up test procedures; food-specific SPT ≥ 3 mm or food-sIgE $\geq$ class 1; all without a clear-cut negative case history, i.e., the child regularly consumed the culprit food without any symptoms (11). Standardized oral challenges were performed in children suspected with FHS according to EAACI guidelines (6). Adverse reaction to food was classified according to the revised nomenclature (1) and further divided into non-allergic FHS and allergic FHS, when immunological mechanisms were demonstrated, i.e., at least one positive test result (SPT or s-IgE).

The standardized open food challenge (OFC) (6) was performed in all children ≤ 3 years of age, whereas the double-blind placebo-controlled food challenge (DBPCFC) was performed in children > 3 years of age. OFC was performed with unmasked hen's egg, cow's milk, peanut, soy, coloring agents, kiwi, tomato, hazelnut, orange, Brazil nut, codfish, cod roe, chocolate, ketchup, and strawberry jam given in increasing doses according to guidelines. DBPCFC was performed with peanut, shrimp, cow's milk, and hen's egg, all masked as previously described (11) and administered in increasing doses according to guidelines. Vehicle foods were used as placebo reference. A positive challenge was classified as immediate (≤ 2 h) or late reactions (> 2 h). All participants were examined for late reactions by telephone interview.

Atopic dermatitis

Atopic dermatitis was diagnosed according to Hanifin-Rajka criteria (18). Four minor criteria were excluded; keratoconus and anterior subcapsular cataract (requiring an ophthalmologist), early onset because of age of study population (infants) and white dermographism/delayed blanch which is nonspecific in a pediatric population (19).

Data management and statistics

All children were rechallenged every 6 months according to guidelines (6). A child with a positive challenge was considered food hypersensitive until the first negative challenge with the same food type occurred. All children with FHS were plotted in a Gantt diagram and the accumulated number of children with FHS was calculated at each follow-up. All data from recruitment to the 18 months follow-up was double-entered into a Microsoft Access Database, whereas every tenth dataset from the 36 and 72 months follow-up were double-entered. Because of the relatively small numbers in disease groups, no stratification was possible. Difference between groups was calculated with Chi-squared test. Statistical Analyses were performed by STATA 10.0 (Stata Corp., College Station, TX, USA). The study was approved by the Ethics Committee for Vejle and Funen Counties (#: 19980102) and informed consent was obtained from the parents.

Results

During the 6 years, 65 children (12%) reported AD, urticaria or rhinitis when foods, mainly cow's milk, hen's egg, peanut, or wheat were ingested. Of these, only 30 children had a clinical history indicating FHS, but additionally 36 children had a positive SPT of s-IgE without a clear-cut negative case history. In all, 66 children underwent 120 challenges with 16 foods during the 6-year period of which 112 were open and 8 were DBPCFC throughout the 6 years (Table 2). Furthermore, 17 challenges were omitted because of lack of patient/parent compliance, contraindications or expected severe symptoms. Sixteen of these were considered to be positive and were included in further analysis. Milk, egg, and peanut accounted for 69% (95/137) of all challenges. Thirty-seven challenges resulted in immediate reactions, mainly urticaria and pruritus. Two children reported late-phase reactions; one of them, isolated late-phase reaction

Table 2. Oral food challenge in the DARC cohort 0–6 years of age

	Total foods*	Milk	Egg	Peanuts
Challenges performed/indicated	120/137	18/28	48/55	12/12
Positive challenges (omitted challenges considered positive)	39 (16)	8 (9)	27 (7)	4 (0)
Immediate/late reactions	37/2	7/1†	26/1	4/0
Immediate symptoms (≤ 2 h) after milk, egg, and peanut challenge				
Urticaria	26 (70%)	5 (63%)	20 (77%)	1 (25%)
Pruritus	20 (54%)	3 (38%)	13 (50%)	4 (100%)
Erythema	14 (38%)	2 (25%)	12 (46%)	0
Gastrointestinal	13 (35%)	2 (25%)	8 (31%)	3 (75%)
Rhino conjunctivitis	8 (22%)	1 (13%)	7 (27%)	0
Airways	3 (8%)	2 (13%)	0	1 (25%)

DARC, Danish Allergy Research Centre.

*Milk, egg, peanut, shrimp, soy, coloring agents, kiwi, tomato, hazelnut, orange, brazil nut, codfish, chocolate, ketchup, and strawberry.

†Isolated late-phase reactions.

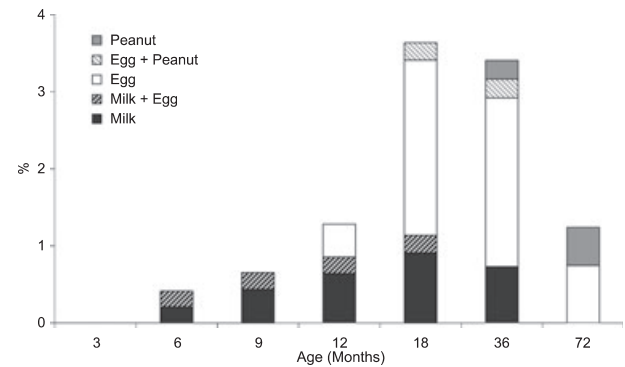


Figure 1. Point-prevalence of challenge-confirmed food hypersensitivity in the DARC cohort and the distribution of different allergens to each follow-up.

(exacerbation of itchy eczema) 48 h after ingestion of milk.

During the 6-year period, 20 children had challenge-confirmed FHS to one or more food types, giving a 6-year incidence of 3.7% (20/534). FHS was first documented at the 6 months follow-up in 2 of 483 children giving a point prevalence of 0.4% (Fig. 1). This increased to 1.3% (6/468) at 12 months, peaked at 18 months (3.6%–16/440), and then decreased to 3.4% (13/441) at 36 months and further to 1.2% (5/404) at 72 months (12).

During the first 12-month lifespan, cow's milk was the most predominant food allergen, accounting for two-thirds of all cases of FHS. From 18 months of age, hen's egg was the major allergen, contributing to more than 60% of all cases. No new cases were detected after 36 months of age. At 72 months, all children had outgrown their milk allergy and 80%, their egg allergy. Peanut hypersensitivity was first shown at 18 months of age. No cases of allergy to wheat, fish, or soy were confirmed.

Of the 20 children with FHS, 18 (90%) were diagnosed with AD at least once during the 6-year period. Furthermore, 104 children were diagnosed with AD in the same period without having FHS, meaning that 14.8% (18/122) of all children with AD had challenge-confirmed FHS at some point.

Sensitization

Of the 501 children who had at least one s-IgE test performed between 3 and 72 months, 146 (29.1%) had more than one positive IgE to egg, milk, peanut, or fish. In addition, 91 children were monosensitized to wheat, which increased the frequency of sensitization to any foods to 47.3%. Of the 237 food-sensitized children, 218 (92%) never developed symptoms following ingestion of foods. The cumulative incidence of IgE-sensitization from birth to 6 years of age was 19.0%, 11.6%, 5.2%, 5.8%, and 31.7% to egg, milk, peanut, fish, and wheat respectively.

Table 3. Classification of children in the DARC cohort according to diagnosis of FHS and AD

Sub-group	n	Description
FHS _{relevant}	20	Clinical relevant sensitization in the 20 children with challenge-confirmed FHS (FHS _{relevant}), e.g. egg-sensitization in a challenge-confirmed egg-allergic child. 18 of 20 children with FHS additionally had AD
FHS _{irrelevant}	20	Clinical irrelevant sensitization in the 20 children with FHS to allergens which the allergic child tolerated (FHS _{irrelevant}). This could be milk sensitization in an egg-allergic child who tolerates ingestion of milk
AD	104	Children with a diagnosis of AD at least once during the 6 years, who never had confirmed FHS
Control	207	Children who had neither AD nor FHS at any of the follow-ups

Children in the cohort were divided into four sub-groups according to the diagnosis of FHS and AD as described in Table 3. Children with FHS were further divided into clinically relevant and irrelevant food sensitization. The frequencies of IgE-sensitization to each follow-up for the four subgroups are presented in Fig. 2A. Nineteen of the 20 children with FHS had s-IgE levels $\geq$ class 2 to the relevant food (FHS_{relevant}) in the same period in which they had positive challenges. The last child had detectable s-IgE level to milk, but below class 1. Lactose intolerance was ruled out in this child. Of the 20 children with FHS, 11 additionally had clinical irrelevant s-IgE $\geq$ class 2 (FHS_{irrelevant}) to egg, milk, codfish, peanut, or soy at least once during the 6-year period. Furthermore, five children had s-IgE

$\geq$ class 1; two of them were monosensitized to wheat. Of the 104 children with AD, 38 (37%) were s-IgE-sensitized to egg, milk, codfish, peanut, or soy; 18 had s-IgE levels $\geq$ class 2. In addition, 16 were monosensitized to wheat, mainly class I, giving a total frequency of 52%.

Children without FHS or AD (control) showed increased sensitization to foods with age; 6% at 3 months to 13% at 72 months. This was mainly because of more frequent class 2 sensitization. The 6-year cumulative incidence of s-IgE sensitization to foods was 30% (52% if wheat was included). The FHS group had significantly more frequently clinically irrelevant s-IgE sensitization compared to both AD and control group ($P < 0.01$). No difference was detected between AD group and control group ($P = 0.24$). The same pattern was found separately for milk, peanut and wheat but not for egg.

Wheat was the food allergen that caused most clinically irrelevant s-IgE sensitization up to 3 years of age. We found a discrepancy between ML and CAP system, which is in line with recent findings (20). Of 40 ML-positive samples reanalyzed, only four were reproducible with CAP. Wheat sensitization in preschool children (21) and adolescents (22) cross-reacts to pollen, especially grass; in children < 3 years, however, this is irrelevant as pollen-sensitization is rare.

Eleven of the 20 children with FHS (55%) had elevated levels of total IgE, i.e., in 3–6 months t-IgE > 15 Ku/l and in 12–72 months, t-IgE > 100 Ku/l. This was significantly different from both AD and control group ($P < 0.01$). Twenty-one of 104 (20%) children from the AD group and 35 of 207 (17%) control children had elevated total IgE; for both groups, the incidence of elevated total IgE increased with age. No statistical difference was documented between these two groups.

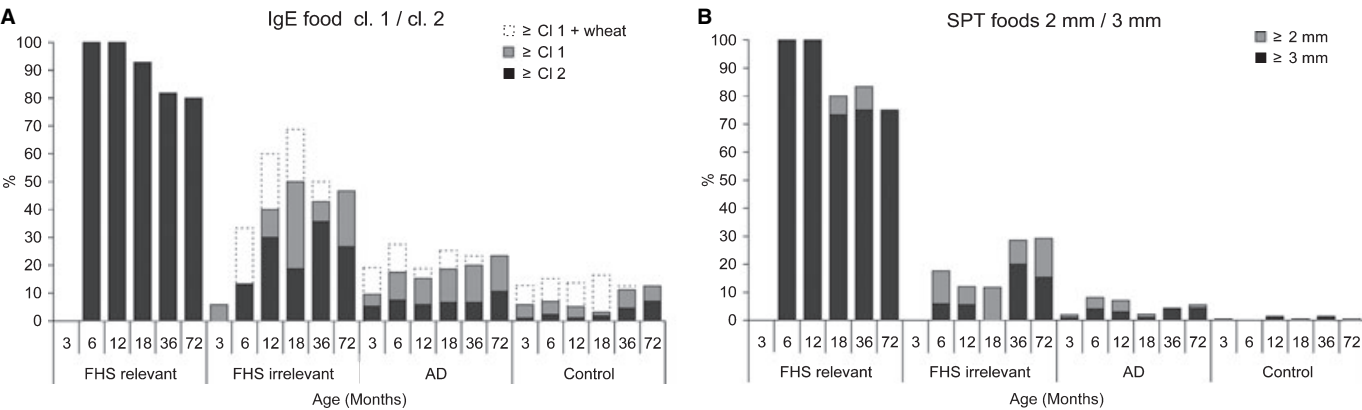


Figure 2. Frequency of s-IgE-sensitization (A) and SPT-sensitization (B) to food-allergens (milk, egg, peanut, fish and soy) in the DARC-cohort. The cohort is divided into 3 distinct groups; a challenge-confirmed FHS-group, a group with at least one diagnosis of atopic dermatitis (AD) and a symptom-free control group. Sensitization in the FHS-group is divided into clinical relevant sensitization (FHS-relevant) and irrelevant sensitization (FHS-irrelevant); i.e. sensitization to foods that children with FHS tolerates. Each bar is divided into s-IgE levels $\geq$ class 1 (grey) and $\geq$ class 2 (black); for SPT, mean wheal diameter ≥ 2 mm (grey) and ≥ 3 mm (black). The dashed line in (A) indicates the frequency of s-IgE levels $\geq$ class 1 if wheat were included. FHS, food-hypersensitivity; AD, atopic dermatitis; SPT, skin prick test; IgE, immunoglobulin E.

Table 4. Specificity (Spec), Sensitivity (Sens), positive predictive value (PPV), and negative predictive value (NPV) of s-IgE and SPT for egg and milk from 3 to 36 months

	PPV/NPV	Sens/Spec
IgE $\geq$ cl. 1	0.34/0.99	0.72/0.95
IgE $\geq$ cl. 2	0.55/0.99	0.63/0.97
SPT $\geq$ 2 mm	0.56/0.99	0.63/0.98
SPT $\geq$ 3 mm	0.70/0.99	0.55/0.98

IgE, immunoglobulin E; SPT, skin prick test; cl.1, class 1; cl.2, class 2; FHS, food hypersensitivity.

Diagnostic values was calculated as FHS^+/FHS^- , where FHS^+ was defined as present FHS or pre-FHS, and FHS^- as FHS never.

Figure 2B presents the frequency of SPT sensitization to foods, measured as mean wheal diameter, according to symptoms in the four groups (as described in Table 3). Nineteen of 20 children with FHS had $SPT \geq 3$ mm to the clinical relevant food type (FHS_{relevant}) and nine had additionally a positive SPT to clinically irrelevant foods ($FHS_{\text{irrelevant}}$). However, only 4 of the 9 children could document repeated SPT to clinical irrelevant foods at more than one follow-up.

Skin prick test sensitization to foods in children without FHS, i.e., the AD and control group was rare; only 2–8% of children with AD and less than 2% of the control group had a positive SPT to foods. Egg was the allergen that caused the most positive SPT in both groups. No SPT to milk was found in these two groups.

Table 4 presents positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity for s-IgE and SPT for egg and milk, measured throughout the first 3 years. The best PPV (0.70) was found for SPT with a cut-off ≥ 3 mm. NPV was 0.99 independent of test and cut-off. The sensitivity for s-IgE test for egg and milk was 0.72 if cut-off $\geq$ class 1 was applied and 0.63 for cut off $\geq$ class 2. Specificity for s-IgE was 0.95/0.97 for $\geq$ class 1/ $\geq$ class 2, respectively, and for 0.98 for SPT, independently of cut-off points. By including wheat $\geq$ class 1 in s-IgE-test, specificity dropped to 0.54 (0.88 if cut-off $\geq$ class 2).

Discussion

Prevalence of FHS

We have documented the prevalence of FHS longitudinally in a population-based perspective cohort. FHS peaks during the first years of life, after which children outgrow most of their food allergies. Point prevalence at 1, 3, and 6 years was 1.3%, 3.4%, and 1.2%, respectively. The spectrum of clinical allergy in this study resembles previous findings (4, 7, 21, 23) i.e., most children are monosensitized. Four of 20 of children with FHS were reacting to two allergens.

Point prevalence of FHS to any foods in children has previously been estimated in population-based cohorts to

1–8% (4, 7, 21, 23). The highest prevalence of FHS in this study was found to be 3.6% at 18 months of age.

Hen's egg was the most frequently eliciting food in our cohort. At 18 month of age, 2.4% of the children had documented egg allergy, decreasing to 1.9% at 36 months, in accordance with the finding of Eggesbo (24) (1.6% at 2½ years of age) and Venter (7) (1.8% at 1 year; 1.0% at 3 years).

Cow's milk protein seems to be the first major allergen that causes hypersensitivity in children and also the most frequently reported allergenic food; 0.5–5.2% (3, 4, 7, 25). Cow's milk allergy peaked at 18 months of age with a prevalence of 1.0% and all children had outgrown their milk allergy at 6 years of age. Peanut allergy in children seems to be rare; prevalence is estimated to be 0.5–1.2% (7, 26, 27) which is similar to our findings.

Discrepancy between self-reported and confirmed FHS

Approximately one-third of self-reported FHS have been confirmed by oral challenges in other studies (3–5), varying with age, study design, and food type (7, 23, 24, 28, 29). We found that 31% (20 of 65) of all self-reported FHS during the 6-year period could be confirmed by challenge. Our results also confirm that the frequency of self-reported FHS decline with age (28). It is a striking feature that 76% of all parentally perceived adverse reactions to food are only reported once during the 6-year period, despite the frequent follow-up rate. Eggesbo (30) found similarly that approximately two-thirds of a Norwegian birth cohort only reported adverse reactions to food once.

Frequency and relevance of sensitization

Sensitization to foods in the DARC cohort in the age group, 0–18 and 72 months, has previously been published (12, 31); however, this was not correlated to FHS. In this study, all adverse reaction to egg was s-IgE mediated, which is in line with other birth cohort studies (23, 24). Moreover, we found that 5 of 6 children had IgE-mediated adverse reactions to cow's milk. This is higher than reported in other studies (3, 5, 7, 21, 23). It remains unclear whether the discrepancy between our and other studies is caused by the small numbers of milk allergic children or because of different sensitization test (SPT or s-IgE). Children with FHS were additionally more frequently sensitized and had higher levels of s-IgE to irrelevant food allergens than children without symptoms to foods. Sixteen of 20 children with FHS were sensitized to clinically irrelevant foods. Confirmation of one food allergy + relevant sensitization in a child does not imply clinical relevance of other sensitization *per se*; those must be confirmed separately.

The role of FHS in children with AD is controversial. Monosymptomatic, late-phase eczematous reactions after food ingestions are rare (32, 33). The combination of early, non-eczematous reactions (urticaria, pruritus, and

oral allergy syndrome) followed by late-phase flares of eczema is presumably more common; however, the challenge-regimen with massive loading of allergen could prevent this as challenges will be terminated after the initial symptoms. We found that 18 of 122 (14.8%) children with AD had FHS, whereas previous studies have reported more than 30% (4, 8–10). However, these studies were mainly conducted on selected children recruited from university clinics.

In our study, children with AD were divided into those with and without FHS, respectively. Based on a 6-year period, we found that children with AD, but without FHS neither were more frequently IgE-sensitized nor had higher levels of IgE than healthy control children (52% 3.2 SU/ml vs. 52% 3.9 SU/ml); they are, however, more persistently sensitized. Only the group of FHS was more frequently sensitized and presents higher levels of IgE. This means that sensitization to foods in young children without symptoms is a normal phenomenon, which additionally results in low PPVs for both s-IgE and SPT to milk and egg (Table 4).

Conclusion

Prevalence of FHS in the DARC cohort peaks at 18 months of age (3.6%). Milk allergy is predominant within the first year of life followed by hen's egg. Peanut allergy was first documented from 18 months of age. Most children react to one allergen and none to wheat, soy, or fish. The discrepancy between sensitization, self-reported food-related symptoms and confirmed FHS illustrates the need to combine parental reporting, clinical examination and relevant sensitization with standardized oral challenge in order to establish diagnosis. Most adverse reactions to food in children are IgE-mediated, and the majority of children with FHS (16 of 20) are additionally sensitized to foods, which they tolerate. Almost all children with FHS have AD, but less than 15% of children with AD have FHS. Half of all children never had symptoms to ingested foods are temporarily sensitized to food allergens; subsequently, sensitization to food seems to be a normal phenomenon in young children without food allergy.

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