

REGULAR ARTICLE

Reported symptoms of food hypersensitivity and sensitization to common foods in 4-year-old children

Eva Östblom (eva.ostblom@ki.se)^{1,2,3}, Magnus Wickman^{1,3,4}, Marianne van Hage^{3,5}, Gunnar Lilja^{1,2,3}

1.Department of Pediatrics, Sachs' Children's Hospital, Stockholm, Sweden

2.Department of Clinical Science and Education, Karolinska Institutet, Stockholm, Sweden

3.Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden

4.National Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

5.Clinical Immunology and Allergy Unit, Department of Medicine, Karolinska Institutet and University Hospital, Stockholm, Sweden

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Correspondence

Eva Östblom, M.D., Department of Pediatrics, Sachs' Children's Hospital, S - 118 83 Stockholm, Sweden.

Tel: +4686164000 |

Fax: +468304571 |

Email: eva.ostblom@ki.se

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Abstract

Aim: To characterize reported food hypersensitivity (FHS) among young children in a birth cohort.

Methods: At 4 years of age a parental questionnaire on FHS and allergic symptoms was evaluated.

Blood was collected for analyses of IgE-antibodies to egg, milk, fish, wheat, peanut and soy. Complete questionnaire data was available for 3694 children (90%), and blood samples were obtained from 2563 children (63%).

Results: FHS was reported in 11% of the children ($n = 397$). Eczema was the most commonly reported symptom and the only symptom in half of these children. Food-related reactions from the airways, facial oedema or urticaria were reported in 198 children, and the majority of these children (75%) reported multiple symptoms. Furthermore, a combination of airway symptoms, facial oedema or urticaria together with sensitization to food suggested a more severe form of FHS. This was found in 1.6% of all children. Symptoms caused by peanut were closely associated with sensitization to peanut ($p < 0.001$).

Conclusions: FHS in 4-year-old children with any of asthma, rhino-conjunctivitis, facial oedema or urticaria in combination is in most cases associated to sensitization to food. This phenotype of FHS is likely to represent a more severe form of FHS.

INTRODUCTION

Four to eight percent of children in the Western world suffer from food allergy verified with oral challenges (1–4), whereas in epidemiological studies based on self-reported data, around 20% are considered to have food allergy/hypersensitivity (2,4). To date, no attempt has been made to estimate severity of reported food hypersensitivity (FHS) in a population-based material, even though suggestions of severity grading in patient-based settings exist in the literature (5,6).

The prevalence of peanut allergy is increasing in some countries (7–8), but otherwise there are few reports of an increased prevalence of reactions towards food allergens among children. The absence of data might be explained by difficulties establishing uniform criteria (9–10), but also by the fact that food allergy varies considerably with age (11–12).

In childhood, hypersensitivity reactions to food are often mediated via the development of IgE antibodies (IgE-ab) (3,13). However, young children may have low levels of allergen-specific IgE-ab to food allergens without showing any signs of allergy (3,14–17). Although IgE-mediated reactions to food allergens are common early in life, adverse reactions to food also frequently arise through other mechanisms, both immunologic and nonimmunologic, many of which are still poorly understood (18,19). This further complicates diagnosis.

In light of the difficulties diagnosing food allergy in children there is a demand for increased knowledge of FHS. The aim of this study was therefore to describe reported FHS in relation to symptoms, food-specific IgE-ab and number of foods involved among 4-year-old children in a large birth cohort BAMSE [Children, Allergy and Milieu in Stockholm, an Epidemiological study (Swedish: Barn, Allergi och Miljö i Stockholm, en Epidemiologisk undersökning)].

MATERIAL AND METHODS

Study design

A birth cohort (BAMSE) of 4089 children was established in Stockholm, Sweden. Detailed data on exposures and parental allergy were obtained through a parental questionnaire when the children were 2 months old (median age) as described in detail elsewhere (20–23). Questionnaires focusing on symptoms related to allergic disease including questions on reactions to foods were sent out to the parents when the children were 1, 2 and 4 years of age with response rates of 96%, 94% and 91% respectively.

Questionnaire data were available for 3742 children at 4 years (92%). These children were invited to a clinical investigation in 1999 or 2000 and 2965 agreed to participate. Blood samples were obtained from 2614. No significant differences in demographic factors, in parental allergy, or in prevalence of allergic disease were observed between the children from whom blood samples were obtained and

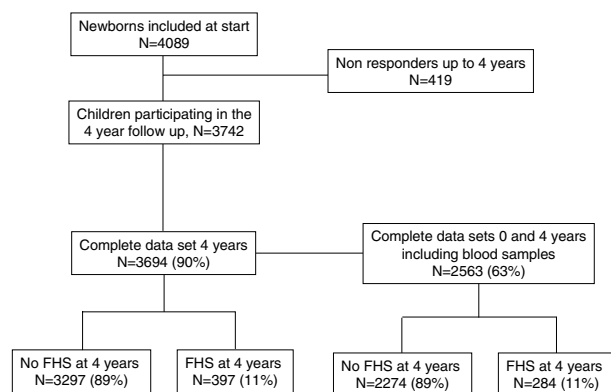


Figure 1 Flow chart of the study population. *Food hypersensitivity.

those who declined blood sampling. All analyses in this study are based on children with complete questionnaire data at 2 months and at 4 years of age ($n = 3694$). Analysis encompassing sensitization to food comprise children with complete questionnaire data and from whom blood samples were obtained ($n = 2563$; see Fig. 1).

Ethical approval was obtained from the Ethics Committee of Karolinska Institutet, Stockholm, and informed consent was obtained from the parents.

Classification of FHS at 4 years of age

Any of the following parentally reported symptoms related to ingestion of a certain food were defined as FHS: asthma, itchy eyes and/or runny nose, oedema of lips/eyes, urticaria, eczema or vomiting/diarrhoea.

Allergen-specific IgE antibodies in plasma were measured against a mix of common food allergens (fx5[®]; cow's milk, egg white, cod fish, peanut, soybean and wheat; ImmunoCAP System, Phadia AB, Uppsala, Sweden). An IgE-antibody level ≥ 0.35 kU_A/L was considered positive. Serum samples that scored positive for fx5[®] were further analyzed towards the individual allergens included in the mix.

Statistical methods

Prevalence in percent and total numbers, and when appropriate with 95% confidence intervals. Differences in proportions between groups were tested with Chi-square test or with proportionality test when appropriate. Levels of IgE-antibodies are given as geometric means. A p -value < 0.05 was considered as significant. All analyses were performed using STATA 9.2 (Stata, College Station, TX, USA).

RESULTS

At the age of four, 397 of the children (11%) in the study group ($n = 3694$) were reported to have symptoms of FHS during the previous 24 months. The distribution of exposures and background factors such as parental allergy, sex, exclusive breastfeeding, early exposure to environmental tobacco smoke or furred pets did not differ significantly between dropouts and children remaining in the study (data not shown). The same variables were equally distributed

Table 1 Foods reported to cause symptoms of FHS in a birth cohort of 2563 children at 4 years of age

Specific foods reported to cause FHS	Children with FHS at 4 years of age, $n = 397$		
	(n)	(%)	CI 95%
Cow's milk	129	32	(28–37)
Citrus	127	32	(27–37)
Peanut	102	27	(21–30)
Tree nuts/almond	98	25	(20–29)
Egg	94	24	(19–28)
Stone fruit	86	22	(18–26)
Chocolate	67	17	(13–21)
Fish	42	11	(8–14)
Pea	32	8	(5–11)
Soy bean	30	8	(5–10)
Wheat	19	5	(3–7)
Banana	7	2	(0–3)

among children with FHS and children without FHS with the exception of parental allergic disease which was more common among children with FHS, 56% (51–61%) as compared to 39% (38–41%) among children without FHS.

Other allergic diseases were, as expected more common among children with FHS. Asthma was found in 16% (12–20%), rhinitis in 30% (25–34%) and eczema in 49% (45–54%). The corresponding figures for children without FHS were for asthma 6% (5–7%), rhinitis 8% (7–9%) and for eczema 17% (16–18%). Thus, differences between FHS and non-FHS children were all statistically significant.

Specific food items reported to cause FHS are presented in Table 1. The most common foods were milk and citrus (both 32%) followed by peanuts (27%) and tree nuts (25%).

Reactions to food

Eczema dominated as reported symptom of FHS, followed by vomiting/diarrhoea, urticaria, oedema of the lips or eyes, itchy eyes and/or rhinitis and asthma (Fig. 2). Of 397 children, 166 (42%) reported multiple symptoms (at least 2 symptoms) of FHS, and this was most common among children with food-induced asthma (95%) and itchy eyes/rhinitis (89%). In contrast, 51% of children with eczema and 45% of children with vomiting/diarrhoea reacted with only one symptom. Interestingly, multiple symptoms were reported in 49% (CI 42–55%) of the boys and in 34% (CI 27–41%) of the girls. However, parental allergic disease did not affect presence of multiple symptoms significantly.

Sensitization

Three hundred and ninety-seventy children (15%) exhibited allergen-specific IgE-antibodies to the selected foods. Detailed data on sensitization are presented in Table 2. Presence of allergen-specific IgE-ab to any of the single foods tested was significantly more common in children with FHS, 34%, (28–39%), than without 13%, (12–15%). Peanut was the most frequently sensitizing food allergen among

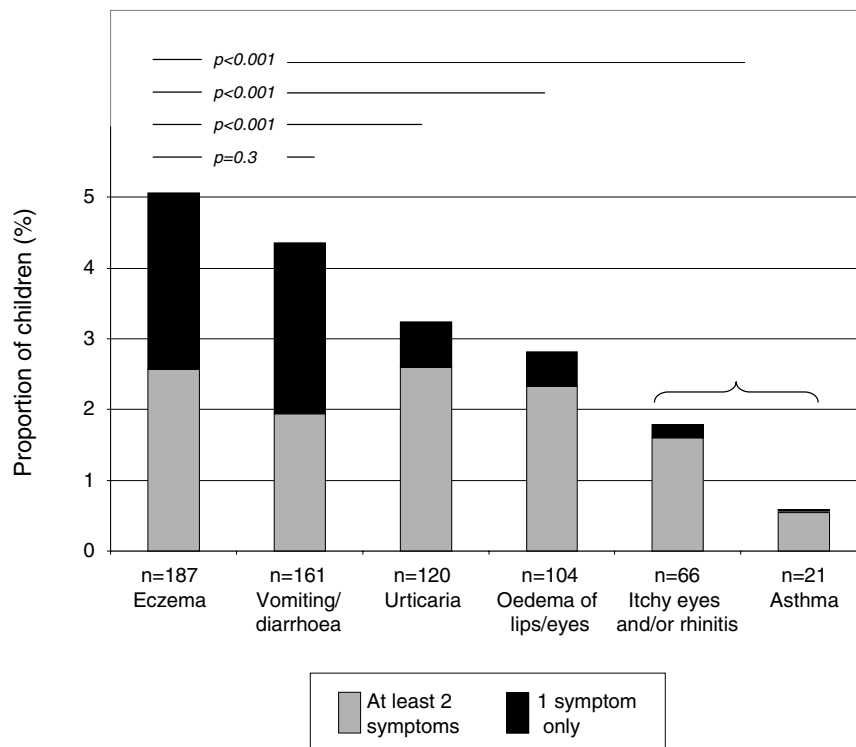


Figure 2 Reported symptoms of FHS at 4 years of age in a birth cohort of 3694 children. The p-values illustrate the statistical differences in proportion of children with multiple symptoms with eczema as the reference symptom.

Table 2 Sensitization to food among 4-year-old children of a birth cohort where blood samples were available (n = 2563)

Allergen-specific IgE antibody level ≥ 0.35 kU _A /L	Children with FHS (n = 284)		Children without FHS (n = 2279)		Total (n = 2563)	
	(%)	CI 95 %	(%)	CI 95 %	(%)	CI 95 %
Any of the tested foods	34	28–39	13	12–15	15	14–17
Cow's milk	16	12–21	7	6–8	8	7–9
Hen's egg	15	11–19	3	3–4	5	4–6
Cod fish	4	1–6	0	0–1	1	0–1
Peanut	22	17–27	3	3–4	5	4–6
Soy bean	14	10–18	2	1–2	3	2–4
Wheat	12	8–16	3	2–3	4	3–4

children with FHS. The geometric mean for milk-specific IgE-antibodies among children sensitized to food with report of milk-related symptoms was 3.2 kU_A/L (1.5–6.6). The corresponding value for egg was 2.0 kU_A/L (1.2–3.3), for fish 1.0 kU_A/L (0.5–2.1), for peanut 8.8 kU_A/L (5.1–15), for soy bean 2.4 kU_A/L (0.6–9.5) and finally for wheat 6.6 kU_A/L (0.5–8.4). For children sensitized to food, but not to the food reported to cause symptoms, the geometric mean values ranged from 0.4–0.9 kU_A/L. Among children with at least two of urticaria, asthma, facial oedema or rhinoconjunctivitis, suggesting a severe form of FHS, 40/57 (70%) were sensitized to food. This corresponds to 1.6% of all children in the cohort, and the geometric mean for food-specific IgE (fx5®) in this group was 9.6 kU_A/L. Sensitization to food was more frequently found among boys with FHS, 41% (33–49%), as compared to girls, 25% (17–32%). Parental allergy

did not significantly affect the presence of sensitization to food.

The association between reported food-related symptoms and any of the six tested foods and sensitization to the offending food was also evaluated (Fig. 3). Among children with report of FHS peanut was the most common sensitising offending food. In children with report of FHS caused by milk only 25% were sensitized to milk. Using sensitization to milk in relation to reactions to milk as a reference, a significantly larger proportion of children sensitized to peanut or egg showed associations to the respective foods.

The relationship between specific symptoms and sensitization to the offending food among children with FHS is presented in Figure 4. Children with food-related oedema of lips/eyes, itchy eyes/rhinitis or asthma were significantly more often sensitized to the offending food as compared to

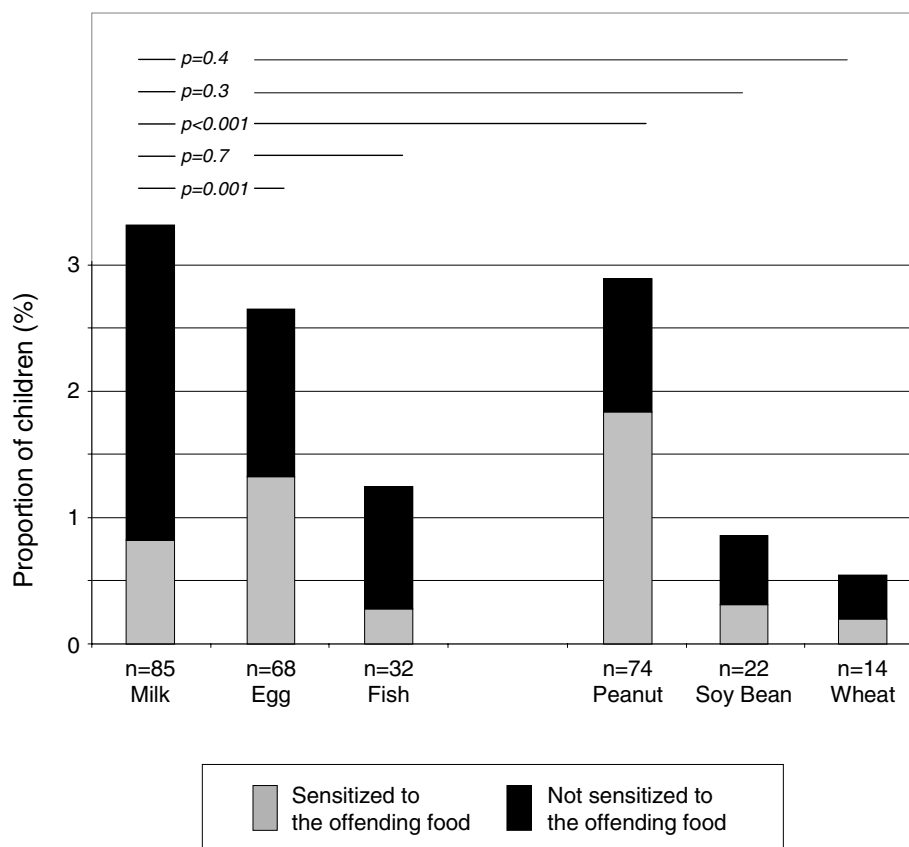


Figure 3 Specific foods reported to cause symptoms in children with FHS in relation to sensitization* to the same food. The p-values illustrate the statistical differences in proportion of children sensitized to the offending food with milk as the reference food. *Specific IgE-antibodies $\geq 0.35 \text{ kU}_A/\text{L}$.

children with food-related eczema ($p < 0.05$, $p < 0.001$ and $p < 0.01$, respectively). No significant difference in this respect was seen comparing eczema with vomiting/diarrhoea or urticaria. Only 10% of children with vomiting/diarrhoea as isolated symptoms of FHS were sensitized to food.

DISCUSSION

There are few cohort studies on the prevalence of food-induced allergy/hypersensitivity among young children. In our study, with 3694 children (90%) still remaining in the birth cohort at 4 years of age, the prevalence of perceived FSH at this age was found to be 11%. Other cohort studies have shown a similar or even higher prevalence (1,2,4,24). In our study, eczema and vomiting/diarrhoea were the symptoms most commonly reported. The majority of children with these two symptoms stated only one symptom of FHS. On the other hand, children who were reported to have urticaria, oedema of lips/eyes, itchy eyes and/or rhinitis or asthma reported more often multiple symptoms. These latter symptoms were also more closely related to sensitization to food. These observations suggest that children with food-induced airway symptoms, urticaria and/or facial oedema seem to have a more severe FHS, since such symptoms are more closely associated to sensitization to food and are also more frequently generalized (5,6).

Our results on food sensitization are in agreement with earlier observations among young children living in Norway (4). In a German study by Zuberbier et al., a slightly different pattern of sensitization was seen with a smaller proportion of the total study population being sensitized to food, and only half as many to milk, egg and peanut as compared to our study (24). The apparent discrepancy could be due to use of different methodology, i.e. *in vitro* testing versus skin prick test, but in particular to differences in the age groups studied. In the latter study all ages were included (24).

Among children with vomiting/diarrhoea as the only symptoms of FHS, sensitization to food was not more common than among children without FHS. This indicates that such food-related symptoms alone may not be associated with sensitization to food *per se*, even though the absence of allergen-specific IgE does not exclude FSH. Niggemann et al. has shown that 10% of positive DBPCFC in children with atopic dermatitis are not related to IgE sensitization, indicating that immunological mechanisms other than IgE might be involved in food-induced hypersensitivity (19). This can be compared with 66% in our study with report of symptoms of FSH but without detectable IgE to food. Hence we can not rule out that at least some of the children in our study are suffering from non-IgE-mediated FSH. Furthermore, it is well-known that citrus can aggravate existing atopic dermatitis which is not an IgE-mediated reaction.

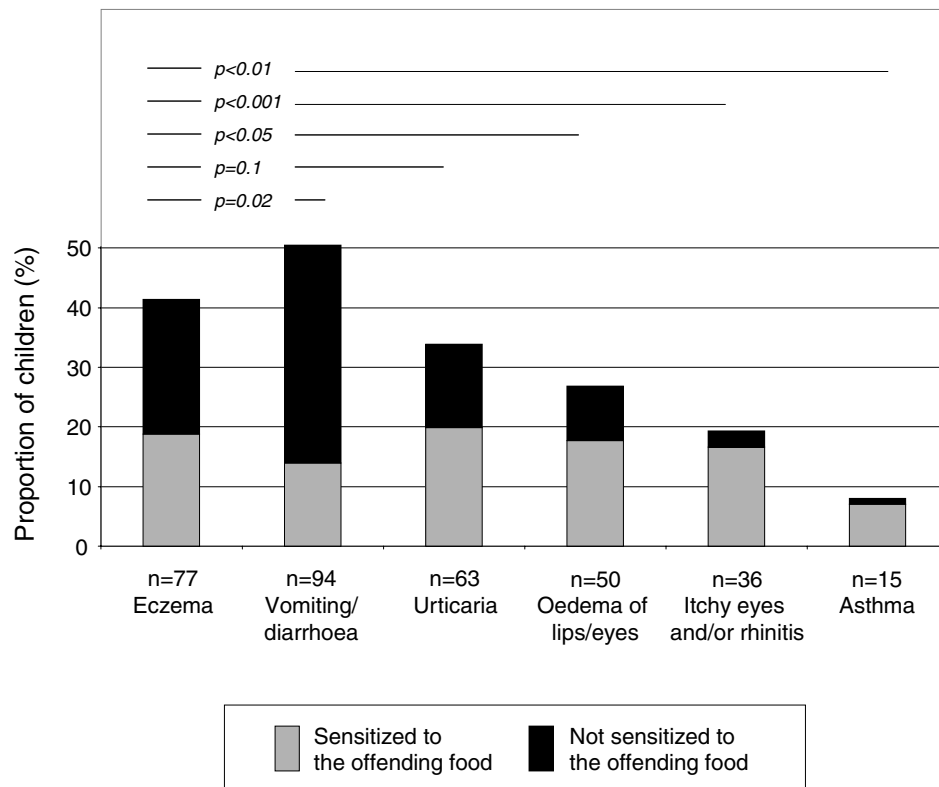


Figure 4 Proportion of children sensitized to at least one offending food in relation to symptoms of FHS. Only children who have report of FHS caused by any of the six foods tested (177/266) are taken into consideration. The p-values illustrate the statistical differences in proportion of children with sensitization to at least one offending food with eczema as the reference symptom.

The association between the specific food reported to cause symptoms, and sensitization to the same food at a cut-off level of 0.35 kU_A/L was rather limited, especially among children with report of eczema and vomiting/diarrhoea. Low levels of allergen-specific IgE antibodies towards food allergens are a common phenomenon during childhood and may lack clinical importance (3,14–17). This emphasizes the need for the use of quantitative measurements of IgE rather than the use of the mere presence of sensitization, as well as for oral challenges for verification of symptoms and for the diagnosis of FHS (15,16,25–28).

The strength of our study is the high participation rate of 90% of the cohort. Objective measurements such as allergen-specific IgE-levels to 6 common food allergens were available among 63% of the children, which makes the study of this size unique. The fact that we analyzed a homogenous age group is another considerable strength since food allergy is a very dynamic process during the first years of life. To our knowledge, no similar study of children at the age of 4 has been published.

We have not performed any food challenges within this study for many reasons but mainly because of the size of the study and the age group. Thus, we were not able to match reported symptoms and levels of IgE-ab to a certain food allergy diagnosis. However, our aim was to investigate dif-

ferent aspects of perceived food allergy and to relate different symptoms of FHS to sensitization to food.

In conclusion, reported FHS is common and was found in 11% among our studied 4-year-old children. Symptoms after ingestion of a certain food such as asthma, rhinoconjunctivitis, facial oedema or urticaria in combination with sensitisation to food, are likely to represent a more severe phenotype of FHS and was present in 1.6% of the studied children. In these children oral challenges may not be necessary. However, in children with eczema and especially vomiting/diarrhoea as the only food-related symptoms present, IgE-mediated food allergy seems less likely. In this category of children with FHS, food challenge may be the only way to verify reactions to food.

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