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Point prevalence and risk factors for food allergy in a cohort of 386 children with atopic dermatitis attending a multidisciplinary dermatology/paediatric allergy clinic*

Background: There is considerable debate about the prevalence and relevance of food allergy (FA) in atopic dermatitis (AD). The aim of this study was to investigate the prevalence of and risk factors for FA in a cohort of children with AD attending a multidisciplinary paediatric allergy clinic. *Methods:* The analysis was performed on 386 children (50.8% boys, median age 4 years) consecutively evaluated for AD. A diagnosis of FA was established on positive skin tests and/or a specific IgE value or a positive oral food challenge. *Results:* Point prevalence of FA was 17.8%. Egg, peanuts, milk, tree nut and mustard accounted for 93% of cases. 37.7% of children had ≥2 positive food reactions. Risk factors associated with FA were young age (OR = 7.9 when ≤2 years compared with ≥5 years), moderate to severe AD (OR = 7.8 for severe and 2.4 for moderate AD) and onset of AD before 3 months of age (OR = 5.7). *Conclusion:* Point prevalence of FA in children with AD is lower than initially reported in patients recruited in a paediatric allergology setting. Children ≤2 years of age with early-onset or severe AD are at higher risk of FA and may be candidates for FA evaluation.

Key words: atopic dermatitis, children, food allergy, prevalence, risk factors

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease in children. Its association with other atopic diseases such as food allergy (FA) has been described. It has been reported that only a third of self reported suspected food allergies could be confirmed by challenge [1]. The relationship between food allergy and atopic dermatitis has raised considerable debate and there is conflicting information concerning the prevalence of FA [2]. In addition, the risk factors for food allergy in AD patients [3] have not been fully characterised [2].

In children with AD, FA investigations are not recommended systematically [2]. It has been shown that personal history is not a good predictor of FA. Personal history recorded by an experienced physician was associated with a positive predictive value (PPV) of 83% and 33% for immediate and late reactions, respectively, and a negative predictive value (NPV) of 74% and 79%, respectively [4]. In our department, a multidisciplinary clinic involving a dermatologist and a paediatric allergist has been held since 1997 for children with AD referred by paediatricians, general practitioners and dermatologists. As part of the investigations for atopic disease, a thorough investigation of food allergy is systematically performed on all children referred to the multidisciplinary clinic. This type of multidisciplinary investigation allows a number of different aspects to be included that may be risk factors for FA.

The primary aim of this study was to estimate the prevalence of FA using stringent criteria in a cohort of children with AD undergoing a multidisciplinary allergological evaluation and to determine the risk factors associated with FA.

Patients and methods

Patients

We evaluated 386 children (0 to 18 years of age) seen consecutively at multidisciplinary clinics from May 2002 to December 2008. The reason for referral in the dermatology department was atopic dermatitis in children requiring specialist advice about AD treatment and/or an allergological evaluation. Parental agreement for allergological evaluation was obtained for all children.

The allergy-dermatology clinic has been run on a bimonthly to monthly basis since 1997. On average, 4 children per week are seen per clinic. Patients are referred to the clinic by community-based dermatologists, paediatricians, general practitioners and allergists. The clinic may be considered a

* This paper is dedicated to the memory of Pr Fabienne Rancé, our friend and colleague, who died while drafting this article.

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tertiary care centre serving a population of about 2.7 million people in the South-West of France. Each clinic is held in the dermatology department, is multidisciplinary and involves a dermatologist allergist (F. Giordano-Labadie) and a paediatric allergist (F. Rancé).

Data collection

Clinical data were collected on a standardised electronic case report form developed by the medical team. The following parameters were systematically recorded: age, sex, age at onset of AD, presence of asthma or other symptoms of allergy (rhinitis, conjunctivitis, suspicion of food allergy), duration of exclusive breast-feeding (exclusive maternal milk without formula milk supplementation), age of food weaning (introduction of food other than milk) and familial history of atopic disease (atopic disease in first-degree relatives).

AD diagnosis

To define AD we used the United Kingdom Working Party's criteria [5]. For clinical examination and severity evaluation, the scoring of atopic dermatitis (SCORAD) index [6, 7]. was applied. AD severity was categorised as follows: mild AD: SCORAD <25, moderate AD: SCORAD from 25 to 50, severe AD: SCORAD >50, as previously reported [8].

Diagnostic work-up of FA

The diagnostic work-up of FA was performed as described previously [9]. A pre-defined decision tree (*figure 1*) using results from skin prick tests (SPT), food atopy patch tests (APT), food specific IgE (s-IgE) and, when appropriate, oral food challenge (OFC) was used to establish the diagnosis of food allergy. Both skin prick tests and atopy patch tests included the most frequent food items in children according to age [10] and additional food items could be added according to the child's clinical history.

Skin prick tests

Oral treatments with antihistamines and systemic steroids were stopped 3 and 7 days, respectively, before skin testing. SPT were performed on healthy skin on the inside of the upper arm and/or forearm. Positive (histamine 10 mg/mL (Stallergenes, Antony, France)) and negative controls and fresh foods or commercial extracts in the case of food items with histamine-releasing properties were used [9]. The following food items were tested systematically:

- in children younger than 2 years: fresh pasteurised cow's milk, fresh white and yolk of hen's egg, fresh soy flour, fresh wheat flour and commercial codfish extract (Stallergenes, Antony, France);
- in children aged 2 to 10 years: fresh cow's milk, fresh hen's egg, fresh roasted peanut, hazelnut (other tree-nuts if positive), fresh sesame seeds, commercial codfish, shellfish, mustard and kiwi fruit extracts;
- in children older than 10 years or in the event of a convincing clinical history: the same food items were tested as in children between 2 and 10 years with the addition of pollen-associated food items such as apple or hazelnut using commercial extracts when available. Additional food items were tested according to clinical history. Readings were taken at 15-20 min. A SPT was considered positive when the greatest diameter of the wheal was 3 mm larger than the negative control, as long as the histamine control

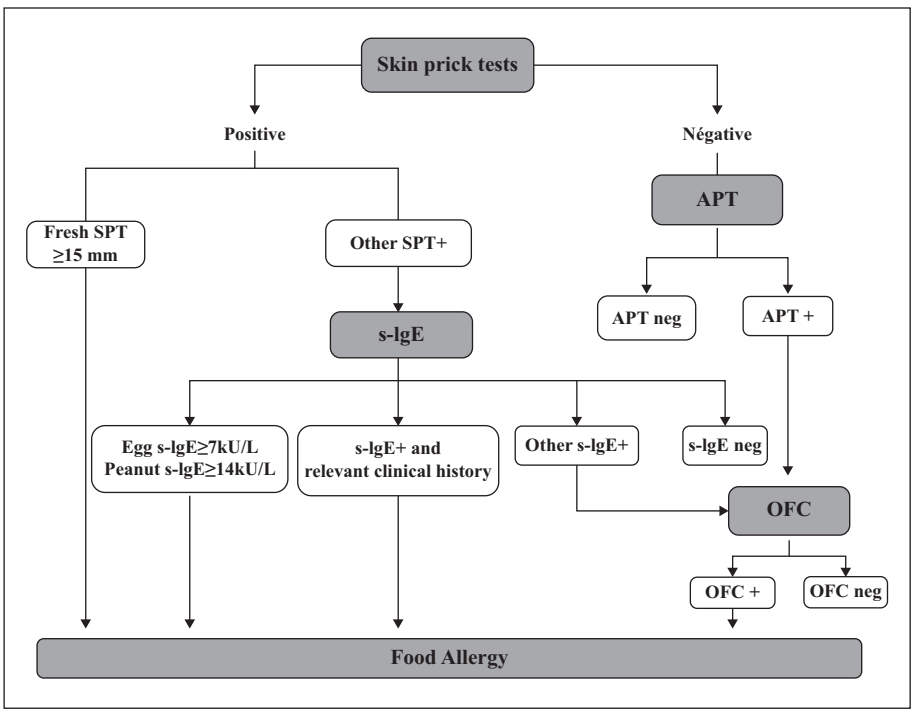

Figure 1. Predefined decision tree for food allergy diagnosis in the study.

prick test was positive. A SPT with fresh food greater than 15 mm was considered as a positive diagnosis of food allergy [11].

Serum-specific IgE assay

Food s-IgE serum levels were assessed in children with positive SPT to food allergens using the ImmunoCAP method (CAP) (Phadia, Uppsala, Sweden). Previous studies have shown that high s-IgE levels to white of hen's egg and peanut are highly predictive of allergy to these food items with a positive predictive value of at least 95% [11]. An oral food challenge was performed to confirm suspected FA according to the algorithm presented in *figure 1*.

Atopy patch tests: investigation of late food allergy reactions

In addition to stopping oral treatment with antihistamines and systemic steroids respectively 3 and 7 days before patch testing, the use of topical steroids and topical immunomodulators was prohibited on test areas 7 days before patch testing [12].
In patients with negative SPT, APT were performed systematically. Patch testing was performed on normal-looking skin on the back with a large (12 mm) cup size Finn's Chamber Test (Epitest Ltd Oy, SmartPractice, Phoenix, Arizona, USA) [13]. APTs to cow's milk (fresh pasteurised semi-skimmed milk), raw mixed hen's egg, wheat flour (1 g diluted in 10 mL of normal saline solution), mixed fresh peanuts diluted in normal saline solution and fresh soy milk were performed.
APT were removed after 48 hours and readings were taken at 48 and 72 hours according to the EEACI (European Academy of Allergy and Clinical Immunology) recommendations [14]. Readings classified as +, ++, +++ or ++++ were defined as positive for an allergic reaction, as opposed to all other readings (negative, doubtful or irritant), which were defined as negative. When the APT was positive, an OFC was performed to establish FA.

Oral food challenge

OFC was conducted under careful medical supervision in the day-care paediatric department adjacent to an intensive care unit. In accordance with current recommendations on surveillance measures, trained physicians and emergency equipment were available to treat severe allergic reactions, including anaphylaxis [15]. Fresh food extracts were used and were the same as those employed for SPT and APT. The suspected food was to be eliminated from the diet 4 weeks prior to OFC on the instruction of a nutritionist. Antihistamines and oral steroids were stopped at least 7 days before challenge. OFC was blinded depending on the child's age: most OFCs were performed double blind in children over three years of age in accordance with current recommendations [11].
The children were observed up to 4h after the last food intake for specific symptoms such as urticaria, angio-oedema, erythema, rhinitis, bronchial obstruction, vomiting and anaphylaxis [16]. A reaction was considered immediately positive if it occurred within 4h of the last intake of the tested food item. Skin reactions occurring after 4 hours were considered late reactions [11]. Parents were interviewed by phone to detect delayed reactions at 24h and during the first 5 days following the challenge. If an immediate reaction occurred during the OFC, a diagnosis of FA was established and no further evaluation was performed. In the case of a negative OFC, parents were advised to allow their child to consume the food again.

FA diagnosis

The diagnostic algorithm used for FA diagnosis in this study is depicted in *figure 1*, it was established on the basis of previously validated and published data [2, 11, 16-19]:

- diameter of wheal of SPT for a given food item larger than 15 mm using fresh food
- or
- predefined threshold of s-IgE for peanut and egg white: the limit for establishing allergy was 14 kU_A/L for peanut and was (7 kU_A/L for egg white in patients older than 2 years and (2 kU_A/L in patients younger than 2 years
- or
- specific symptoms such as urticaria, angio-oedema, erythema, rhinitis, bronchial obstruction, vomiting or anaphylaxis appearing within 4 hours of food ingestion or late reaction (eczema flare-up) within 5 days in association with an OFC

Clinically relevant history was defined as urticaria, angioedema, erythema, rhinitis, bronchial obstruction, vomiting or anaphylaxis appearing within 4 hours after ingestion of an identified single food item.

Statistical analysis

The primary aim of the study was to determine the prevalence of FA in AD with a precision of ± 5%. Based on previous literature, it was estimated that the prevalence of FA in AD would be 40%. A sample size of 365 patients was sufficient to provide an estimate of the point prevalence of FA in children with AD with a precision of plus or minus 5%. Continuous variables were presented as mean, standard deviation (SD) or median interquartile range (IQR) according to their distribution (normal or skewed). Differences between groups (FA *versus* no FA) were compared using a t test or Wilcoxon's rank sum test and a chi-squared test, as appropriate. Logistic regression was used to take into account possible confounding factors. The first model included all the variables that were associated with food sensitisation in a bivariate analysis with a conservative p-value of 0.2. A stepwise analysis in descending order was performed to obtain the best reduced model. First-order interactions were tested at the end of the modelling process.
Model adequacy was checked using the Hosmer and Lemeshow test. Tests were two-sided and p-values less than 0.05 were considered significant. Data analysis was performed using Stata 9.0 software (Stata Corporation, College Station, TX, USA).
The dependent variable was FA and frequency of FA was estimated with a 95% confidence interval. Variables included in the multivariate analysis were gender, age, age at AD onset, AD severity, exclusive maternal breast-feeding, atopic disease in the family and sibling atopy.

Results

Demographic characteristics

Out of 400 patients seen consecutively in the clinic between 2002 and 2008, 386 had a confirmed diagnosis of AD. The median age was 4.0 years (IQR 1.7-7.7) and 50.8% of children were male, males were slightly younger than females (median age of 3.5 *vs* 4.4 years). Age at onset of AD was <3 months for 139 (36.5%) children, between 3 and 12 months for 137 (36%) and >12 months for 105 patients (27.6%). The median SCORAD was 18.7 (IQR 11.5-29.6). Based on SCORAD categorisation, the majority of patients seen in the clinic were patients with mild AD: 247 (67.5%) children had mild, 105 (28.7%) moderate and 14 (3.8%) severe AD.

Results of food allergy assessment (*figure 1*)

Among the 386 evaluated children, FA was diagnosed in 69 children, of whom 26 children had a reaction to more than one food item. The basis for diagnosis of FA in the 69 children with FA can be summarized as follows: eight children had significant positive SPT with fresh food over the predefined diameter wheal, 13 had egg or peanut positive fresh SPT under the predefined diameter but s-IgE over the predefined threshold, 23 had positive SPT with presence of s-IgE and relevant clinical history, 25 had a positive OFC. Among those 25, 22 had positive SPT, s-IgE presence and no relevant clinical history with the suspected food and 3 had negative SPT but positive APT with the food used in the OFC.

Prevalence of food allergy in children with AD

The point prevalence of confirmed FA in children was 17.8% (95%CI: 14.1-22.0). A total of 69 children had a diagnosis of FA, with 48 (69.6%) having AD onset before 3 months of age, 17 (24.6%) between 3 and 12 months, and 4 (5.8%) over 12 months. The most frequent food items involved were hen's egg (n = 59 positive children), peanut (n = 18) and cow's milk (n = 8). The distribution of positive food items is shown in *figure 2*. A total of 26 (37.7%) positive children had two or more positive food reactions, mostly including egg. The most frequent associations found were egg-peanut (n = 15) and egg-milk (n = 6). There was no significant difference between boys and girls in terms of food items involved. Late reactions were observed in 3 cases and confirmed by OFC.

Table 1. Multivariate logistic analysis of risk factors associated with food allergy in 337 children with atopic dermatitis

	Initial model			Final model		
	ORa*	**95% CI****	**p**	**ORa**	**95% CI**	**p**
Gender						
Male	1					
Female	0.93	0.5-1.8	0.83			
Age (years)						
above 5	1					
2-5 years	1.9	0.8-4.8	0.15	2.2	0.9-5.3	0.09
<2 years	7.0	2.8-17.5	$<10^{-3}$	7.9	3.3-19.0	$<10^{-3}$
Age of weaning						
<3 months	1					
>3 months	2.5	0.5-12.1	0.25			
Age at onset of AD						
>1 year	1					
3 months – 1 year	1.7	0.5-6.0	0.39	1.6	0.5-5.5	0.44
<3 months	6.2	1.9-19.9	2.10^{-3}	5.7	1.8-18.3	3.10^{-3}
AD severity						
Mild	1					
Moderate	2.5	1.2-5.1	0.01	2.4	1.2-4.8	9.10^{-3}
Severe	8.7	2.2-35.3	2.10^{-3}	7.8	1.9-31.4	4.10^{-3}
Exclusive maternal breastfeeding***						
No	1					
Yes	1.8	0.9-3.5	0.09			
Atopic disease in family						
No	1					
Yes	1.2	0.6-2.5	0.63			
Brother or sister atopy						
No	1					
Yes	1.2	0.5-2.6	0.62			

**adjusted odds ratio*
***confidence interval*
****forced*

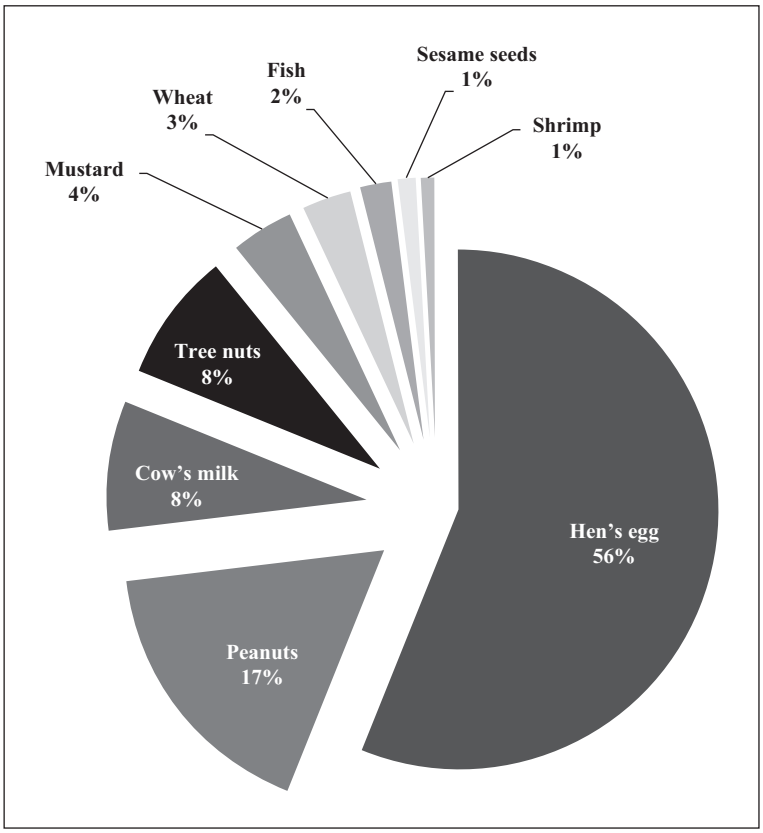

Figure 2. Food items involved in food allergy in children with atopic dermatitis.

Risk factors associated with food allergy in AD

In a bivariate analysis, children with FA were significantly younger than other children (mean age 2.8 *vs* 5.5 years, $p<10^{-3}$). FA was significantly associated with moderate and severe AD (OR = 2.3; 95%CI: 1.3-4.2 and 4.8; 95%CI: 1.6-14.9, $p = 10^{-3}$). The percentage of children with FA in each category of AD severity was 13.5% (33/247) for mild AD, 26.6% (28/105) for moderate AD and 42.8% (6/14) for severe atopic dermatitis. Early onset of AD was significantly associated with FA. When onset of AD occurred before 3 months of age, OR was 13.3 (95%CI: 4.6-38.4). In patients with AD onset between 3 months and 2 years OR was 3.6 (95%CI: 1.2-11.0) compared with children with AD onset over 2 years old ($p<10^{-3}$). FA was also significantly associated with weaning after 3 months of age (OR = 4.5; 95%CI: 1.1-19.3).

Multivariate analysis

The multivariate analysis of risk factors associated with FA in AD is shown in *table 1*. A significant association was found between food allergy and severity of AD (for severe AD, OR = 7.8; 95%CI: 1.9-31.4; $p<10^{-3}$ and for moderate AD, OR = 2.4; 95%CI: 1.2-4.8; $p<10^{-3}$). Children under 2 years of age had a 7.9 times higher risk of having FA diagnosed than children over 5 years (OR = 7.9; 95%CI: 3.3-19.0; $p<10^{-3}$). In addition, early AD onset (<3 months) was significantly associated with FA risk (OR = 5.7; 95%CI: 1.8-18.3, $p<10^{-3}$).

No association was found between FA and gender, exclusive breast-feeding, asthma, age of food weaning, rhinoconjunctivitis or family history of atopic disease.

Discussion

This cohort study in 386 consecutive children with AD shows a point prevalence of FA of 17.8%. Egg, peanut, milk, tree nuts and mustard account for more than 93% of cases. To our knowledge, the present study is the first to analyse the complex relationship between AD severity, AD onset, age and food allergy. Using multiple logistic regression, we were able to disclose that early AD onset, young age and AD severity, as determined by SCORAD, were independent risk factors of FA. Of note, the risk of FA appeared to be strongly severity-dependent. Exclusive breastfeeding and late introduction of food other than milk appeared to have no protective effect on FA risk.

Studies performed in the 1980s and in the 1990s, mostly coming from an allergology setting, have been performed in relatively small cohorts including 40 to about 160 patients [10, 20-23]. In these studies, the frequency of FA varied between 28 and 81% of patients with AD. The high prevalence of FA in these studies may be explained by selection bias and by the use of different criteria to establish FA from

one study to another [2]. Considering that the population of patients with moderate to severe AD is over-represented in the published literature, an overestimation of the frequency of FA in children with AD may have occurred. This is likely to be the case considering, as shown here, that severity of AD is a major risk factor for FA. Unfortunately, it is difficult to compare across studies as severity scoring including a validated tool such the SCORAD, was not uniformly used.
The Danish Allergy Research Centre (DARC) cohort was a population based birth-cohort of 562 children out of whom 122 patients had AD [1]. During a 6 year-period, 14.8% of patients with AD experienced FA as demonstrated by OFC. The severity distribution in the DARC cohort was similar to the present study with fewer than 10% of patients having severe AD [24]. Despite the differences in diagnostic criteria for FA and the duration of observation, there was consistency in terms of FA frequency and food items involved between the present study and the DARC cohort [1].

Food items involved

The food items most frequently responsible for FA in the present study were egg (15.2%), peanut (4.6%), milk (2.1%), tree nut (1%) and mustard (1%). These 5 items enable more than 90% of allergic children to be identified. In published studies on FA in children with AD the following food items were most frequently detected: hen's egg, cow's milk, peanut, wheat and soy; egg was the most prevalent in four studies and the second most prevalent in another four studies; milk, egg, peanut, soy, wheat, cod/catfish and cashew nut accounted for nearly 90% of food allergy diagnoses [1, 4, 10, 18, 20-23]. In the case of egg allergy, this appeared to be the most frequent FA in our cohort, as in the DARC cohort [24]. In previous studies, a restricted number of food items were investigated. Testing tree nut, mustard, shrimp, sesame seeds in addition to common food items, helps to identify allergens which may be important in children. Of note, late reactions to food were rarely observed as only three patients were identified using APT + OFC. The data are in accordance with Rowlands *et al*. [25] who showed that late-phase eczematous reactions after food ingestion are rare. On the other hand delayed cutaneous reaction evaluated with OFC was only performed in patients without immediate reactions according to *figure 1* and some patients may have experienced concomitant immediate and late reactions to food.

Risk factors associated with FA in AD

A strong point of this study was the possibility of exploring risk factors associated with FA in AD based on the prospective recording of AD history and AD severity as evaluated by an experienced dermatologist. Moderate and severe AD identified by the SCORAD index are strongly associated with FA risk. In previous studies on the prevalence of FA in atopic dermatitis, the severity of AD was not consistently recorded [1, 4, 10, 18, 20, 22, 23]. Only two studies used the SCORAD, a validated instrument [4, 6, 24].
There is limited information on the influence of AD severity on FA risk. In a study restricted to late reactions to foods in 64 children with mild to severe AD, no difference in AD severity was found between children with and without FA [4]. It has been suggested that severe eczema was associated with an increased risk of sensitization to egg or other food items and that sensitization to food may increase the risk of severe persistent eczema [26].
Age under 2 was associated with a 7.9 fold increase in the risk of FA. This could be explained by the peak prevalence of FA during the first years of life, after which children outgrow most of their allergies to food [1, 4, 26].
Early onset of AD was described as an independent risk factor for FA in this study. Hill *et al.* [27] have previously shown a higher risk of FA in patients with onset of AD before 6 months of age. We showed that the risk of FA appears to be higher in patients with a very early onset of AD, before 3 months.
We did not find any significant association between exclusive maternal breastfeeding, age of food weaning and risk of FA. The hypothesis that exclusive maternal breastfeeding is a protective factor against atopic disease has long been debated [9]. There is no evidence that exclusive breastfeeding beyond 4 months of age has any effect on the incidence of atopic disease [28]. Interpretation of the data is difficult as reverse causality may have occurred [29]. Although some authors have suggested that exclusive breastfeeding and the use of certain extensively hydrolysed formulas may prevent the development of eczema [30], our study could not find any association between breastfeeding and FA.

Conclusion

Less than a fifth of AD children experience food allergy, with egg, peanut, milk, tree nut and mustard accounting for more than 90% of cases. For most patients food allergy manifests as immediate reactions. Risk factors associated with FA in AD were young age (under 2, OR = 7.9), early onset of AD before 3 months (OR = 5.7) and AD severity (SCORAD over 50, OR = 7.8). In conclusion, AD severity appears to be strongly associated with FA. Children under 2 years of age with early onset or severe AD are at higher risk of FA and may be candidates for FA evaluation. ■

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