Alergia alimentar e eczema atópico: Causa ou consequência?

Food allergy and atopic eczema: Cause or consequence?

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RESUMO

Alergia alimentar (AA) e eczema atópico (EA) surgem frequentemente nos mesmos doentes e partilham a mesma linha cronológica na marcha alérgica. Parte dos doentes com EA beneficiam de avaliação para AA, especialmente lactentes e crianças com EA grave refractário ao tratamento. O diagnóstico de AA em doentes com EA baseia-se numa história clínica cuidada, na interpretação criteriosa dos resultados de testes de alergia e em dietas de eliminação e provas de provocação adaptadas a cada caso. Um diagnóstico rigoroso de alergia alimentar é fundamental para permitir a melhoria das lesões cutâneas e prevenir a restrição alimentar desnecessária. A aquisição de tolerância deve ser avaliada ao longo do tempo, de modo a que os alimentos possam ser reintroduzidos na dieta assim que possível. Especial atenção deve ser dada ao possível subtratamento do EA, estado nutricional e desenvolvimento de AA mediada por IgE aos alimentos evitados.

Palavras-chave: Alergia alimentar, dieta de eliminação, eczema atópico, provas de provocação, sensibilização, testes *patch*, testes *prick*, IgE específica.

ABSTRACT

Food allergy (FA) and atopic eczema (AE) are closely related, often occurring in the same patients and sharing the same timeline in the allergic march. There is indeed a subset of patients with AE that benefit from evaluation for FA, especially infants and young children with severe refractory AE. Diagnosis of FA in children with AE relies on a detailed clinical history, judicious interpretation of allergy tests and specially designed elimination diets and oral food challenges. An accurate diagnosis of allergy to a specific food is crucial to improve skin lesions and prevent unnecessary restriction diets. Acquisition of tolerance should be assessed over time and the foods reintroduced in the diet as soon as possible. Special attention should be drawn to undertreatment of AE, nutritional status and possible development of immediate-type allergy to the avoided foods.

Key-words: *Atopic eczema, patch test, elimination diet, food allergy, food challenge, sensitisation, skin prick test, specific IgE.*

INTRODUCTION

Atopic eczema (AE) is common worldwide, with the highest prevalences reported in Northern European and Australasian countries. Its prevalence in children ranges from 1 to 20%[1] and has increased globally in the recent years[2]. However, changes in prevalence over time differ depending on the age of study population and world region[3]. The prevalence of eczema symptoms has levelled off or decreased in some previously high-prevalence countries, such as the United Kingdom, and has increased in formerly low-prevalence countries, such as Portugal, especially in the younger age groups[3].

AE can result in significant morbidity and negative impact in patients' quality of life[4], with sleep disturbance, school absenteeism, occupational disability and psychological distress, as well as substantial direct and indirect socioeconomic costs[5]. Patients and/or their carers feel the need to find a cause for the development and worsening of skin lesions and very often relate the ingestion of different foods to the relapsing course of eczema. Food allergy (FA) is also suggested as a cause for AE by many primary care providers[6]. A significant proportion of patients suffering from AE end up restricting their diet in some way to try to improve the skin symptoms[7,8], in many cases without seeking for medical advice[9]. This may have consequences on patient's nutritional status, especially in children, where unsupervised dietary restrictions may lead to failure to thrive or even to kwashiorkor or rickets[10]. However, foods can indeed induce symptoms in a subset of patients with AE, in whom judicious allergy testing and dietary avoidance measures may be helpful.

In this paper, we will review the relationship between FA and AE and the current recommendations in the diagnosis and management of FA in patients with AE, attempting to contribute to an improvement in their health care and quality of life.

ASSOCIATION BETWEEN FOOD ALLERGY AND ATOPIC ECZEMA

Different studies have addressed the natural history of AE. Kay *et al*[11] reported that the onset of AE occurs earlier than 6 months of age in 45% and during the first year of life in 60% of children. Williams *et al*[12]

in a birth cohort study showed that among those children who presented with AE by the age of 7, 65% outgrew it at the age of 11, 74% at the age of 16 and 75% at the age of 23. An early onset of AE was associated with the persistence of symptoms in this study. Illy *et al*[13] reported that among those who had an onset of AE before the second year of life, 43.2% were in complete remission by the age of 3, 38.3% had intermittent disease and 18.7% had persistent symptoms. In this study, severity of AE and allergic sensitisation were the major determinants of prognosis. Despite being more common in childhood, AE may have an onset in adulthood[14].

The allergic march

Clinical manifestations of atopy follow a systematic sequence over time – the so-called "allergic march". FA and AE share the same time line, followed later on by respiratory allergies, including asthma and allergic rhinitis (Figure 1). Both the presence of AE and sensitisation to foods in the first 2 years of life seem to predict the future development of sensitisation to airborne allergens and respiratory allergies. Lowe *et al*[15] recently published a birth cohort study showing that sensitisation to food at the age of 6 months was associated with an increased risk of developing eczema up to 7 years of age and that eczema in the first semester of life increased the risk of allergic sensitisation at both 1 and 2 years of age.

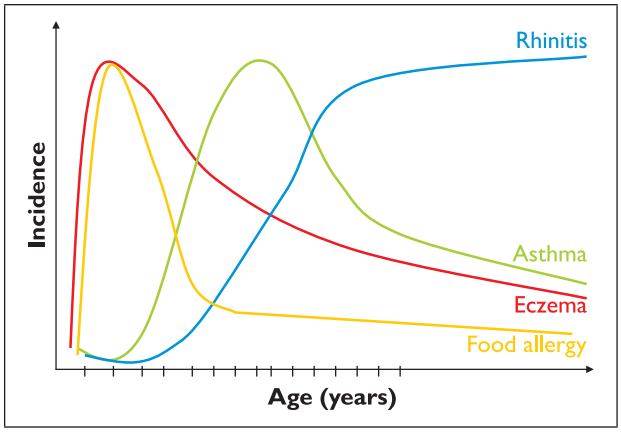


Figure 1. "The allergic march" – Atopic diseases typically follow a chronologic sequence, with atopic eczema and food allergy, usually the first clinical manifestations of atopy, sharing the same timeline.

Prevalence of atopic eczema in food allergy

Although the prevalence of both AE and FA is increasing, there are very few studies looking into the prevalence of AE in patients with diagnosed FA. A recent questionnaire-based case-control study[16] enrolled children referred to a food allergy clinic because of eczema. Children whose parents suspected their child had peanut allergy were excluded. The families were asked to complete a questionnaire and received routine care including consultation with an allergist and allergy testing. Cases were the children who subsequently had a firm diagnosis of peanut allergy, based on weal diameter on SPT to peanut above 8 mm, specific IgE antibody level above 15 KU/L or double-blind-placebo-controlled-food-challenges (DBPCFC) to peanut. High-risk controls were those with a confirmed egg allergy (defined as per peanut allergy) who were not sensitised to peanut. Low-risk controls were children attending the general paediatric clinic with a non-allergic complaint. The groups were similar for age, sex, socio-economic status and breast-feeding. The prevalence of AE in the first year of life was very high among cases (91.7%) and high-risk controls (88.1%) and significantly less so among normal controls (42%), in whom the eczema was also significantly later in onset and less severe.

Prevalence of food allergy in atopic eczema

Conversely, different studies have evaluated the prevalence of FA in children with AE (Table 1), ranging from 33 to 81% as diagnosed by DBPCFC[17-28]. Guillet *et al*[19] first associated the severity of AE with sensitisation to foods. Hill *et al*[26,28] showed a greater frequency of sensitisation and adverse reactions to foods with increasing severity of AE and established a relative risk of IgE-mediated food allergy, in an infant with severe AE, at 5.9[26].

Table 1. Studies evaluating the prevalence of food allergy in infants and children with AE

Study	Population	Number of participants	Main foods implicated	Prevalence of sensitisation to foods	Prevalence of food allergy
Sampson 1985[17]	Severe AE referred to an Allergy Clinic	113	CM, HE, P	–	56%*
Burks 1988[18]	Mild to severe AE	46	CM, HE, P	61%[b]	33%*
Guillet 1992[19]	Severe AE	88	–	93%[b]	–
Sampson 1997[91]	AE referred to an Allergy Clinic	196	CM, HE, P, S	CM=48%[a] HE=74%[a] S=17%[a] P=69%[a] W=12%[a] F=27%[a]	CM=28% HE=45% S=16% P=10% W=10% F=6%
Burks 1998[20]	AE referred to an Allergy Clinic	165	CM, HE, P, S, W, F, cashew	60%[b]	38.7%*
Eigenman 1998[21]	AE referred to a Dermatology Clinic	63	CM, HE, P	65%[b]	37%
Niggemann 1999[22]	Moderate to severe AE referred to an Allergy Clinic	107	HE (accounted for 70% of FA)	56%[a]	81%*
Eigenmann 2000[23]	AE referred to an Allergy or a Dermatology Clinic	74	CM, HE, P	59%[b]	33.8%
Hill 2000[24]	Birth cohort of children with a family history of atopy (24% AE)	559	CM, HE, P	22% at 6 M[b] 36% at 12 M[b]	–
	Subgroup with severe AE	41		83% at 6 M[b] 65% at 12 M[b]	–
Roehr 2001[25]	Young children with AE	98	CM, HE	CM=55%[a] HE=37%[a] W=21%[a] S=12%[a]	CM=46%* HE=28%* W=18%* S=4%*
Hill 2004[26]	Birth cohort of children with a family history of atopy (28.9% AE)	487	CM, HE, P	70%[b]	–
Hill 2007[27]	Moderate AE referred to a Dermatology Clinic	51	CM, HE, P	86%[b]	–
Hill 2008[28]	AE attending specialised clinics in multiple centres	2184	CM, HE, P	48.6%[a]	42.7%†

* Food allergy diagnosed by positive DBPCFC; † This percentage corresponds to the proportion of children with "high-risk IgE food sensitisation", i.e. high specific IgE levels to foods and no adverse reaction reported or no exposure to the food; [a] – food sensitisation detected by serum specific IgE (different decision points were used in different studies); [b] – food sensitisation detected by SPT; M – months of age; CM – cow's milk; HE – hen's egg; P – peanut; W – wheat; S – soy; F – fish

More recently, the association between food allergy (as diagnosed by specific IgE levels above the cut-off for 95% positive predictive value), early onset and severity of AE was confirmed in a larger cohort of young children with eczema assessed between 11.5 and 25.5 months of age[28]. In this international study[28], up to 64% of children whose AE started before 3 months of age were allergic to cow's milk and/or egg and/or peanut. The frequency of "high--risk IgE-food-sensitisation", which was predictive for FA, was greatest in children whose AE started in the first 6 months of life and decreased with increasing age of onset of AE. When AE commenced before 12 months the frequency of FA increased with increasing AE severity, whilst when it started after 12 months of age, the overall frequency of FA was only 22% and the relationship between increasing severity of AE and increasing frequency of allergy to foods was lost. In a regression analysis correcting for potential confounding factors, children with FA had the most severe eczema and the youngest age of onset. Therefore, young infants with AE developing in the first six months of life are more at risk of developing FA.

Summary: *FA and AE are closely related, particularly in childhood: they often occur in the same patients and share the same timeline in the allergic march. Although there is no causality, the prevalence of FA is increased in children with AE. Similarly, the prevalence of AE is increased in children with FA. The prevalence of FA in patients with AE varies with patients' age and severity of AE, being greater in younger children (especially in infants less than 6 months of age) with more severe AE and fine steroid usage.*

ROLE OF FOOD ALLERGY IN ATOPIC ECZEMA

There is growing body of evidence from clinical and laboratory studies to support the association between FA and AE and to document, on one hand, the role of allergy to foods in the pathogenesis and exacerbations of AE and, on the other hand, the role of AE in the development of FA. The two entities may share pathogenic factors, namely genetic, immunologic and environmental factors, although the exact mechanisms are not completely clear. Clinical evidence of the relationship between FA and AE arises from oral provocation and interventional studies.

Eczema exacerbations are reproducible on oral food challenges

For the last 30 years, oral food challenges (OFC) have been used in different studies to demonstrate that a culprit food can induce symptoms in a subset of children with AE (Table 2). The skin symptoms may be immediate or delayed in onset, and may assume different forms, namely skin erythema and pruritus or eczematous reactions of increasing severity with maintained ingestion of the culprit food.

In a population of children with suspected food allergy, Bock *et al*[29] showed that 15% reported eczema as a manifestation of FA and half of these developed exacerbation of eczema during DBPCFC with the culprit food (egg, cow's milk or peanut). Sampson *et al*[17,21,30] have published similar studies in which more than 2000 OFC have been performed in more than 600 children with AE. About 40% of OFC were positive, with skin symptoms in 75% of them, consisting of pruritic, morbilliform or macular eruptions in the predilection sites of AE. Reactions to cow's milk, egg, wheat and soy accounted for about 75% of positive OFC. Although OFC were performed with previous control of the skin lesions, it was observed that a subset of patients who were submitted to daily OFC with repeated reactions had increasingly severe AE.

Isolauri *et al*[31] performed oral cow's milk challenges in 183 children with AE. Fifty four percent of the OFC were positive, 51% with delayed-onset eczematous reactions. Niggemann *et al*[32] performed a similar study in children with AE and suspected FA. Fifty three percent of DBPCFC were positive, 23% of which with late-onset eczematous reactions and 24% with combined early and late reactions which included exacerbation of AE. Previously, Niggemann

Table 2. Main oral food provocation studies in children with AE and/or suspected FA

Study	Population		Culprit foods	Positive OFC	AE exacerbation on OFC
Bock 1978[29]	68 patients with suspected FA age 5M – 15Y	< 3Y (n=25)	CM, HE, P	13/25 (52%)	3/13 (23%)
		≥ 3Y (n=43)		16/43 (37%)	2/16 (12.5%)
Sampson 1985[17]	113 patients with severe AE age 4M – 24.5Y		CM, F, HE, P, S, W	101/113 (89%)	63/101 (62%)
Burks 1988[18]	46 patients with mild-severe AE (34% with suspected FA) age 9M – 19.6Y		C, CM, F, HE, P, S, W	15/46 (33%)	NS (96% cutaneous symptoms)
Isolauri 1996[31]	183 children with mild-severe AE age 2 – 36M		CM	99/183 (54%)	50/99 (50%)
Burks 1998[20]	165 patients with mild-severe AE (25% with suspected FA) age 4M – 22Y		CM F, HE, P, S, W, cashew	64/165 (38.7%)	NS (78% cutaneous symptoms)
Eigenman 1998[21]	63 patients with AE (mean SCORAD = 41.8) age 6M – 20Y		CM, HE, F, P, S, W	11/19 (58%)	NS (94% cutaneous symptoms)
Eigenmann 2000[23]	74 patients with mild-severe AE Age 6M – 16Y		CM, HE, F, S, W, barley, oat	6/19 (32%)	NS (93% cutaneous symptoms)
Niggeman 1999[22]	107 children with persistent to moderate AE and suspected FA age 5M – 12Y		CM, HE, S, W	87/107 (81%)	97/116 (84%)*
Niggeman 2001[32]	139 children with mild-severe AE age 2M – 11.2Y		CM, HE, W	111/139 (80%)	52/111 (47%)
Breuer 2004[33]	64 children with AE and suspected FA age 1 – 10Y		CM, HE, S, W	41/64 (64%)	28/49 (57%)*

* Proportion of positive oral food challenges (OFC). *Abbreviations:* M – months of age; CM – cow's milk; HE – hen's egg; P – peanut; W – wheat; S – soy; F – fish; C – chicken; NS – not specified)

and colleagues[22] had published a retrospective study of 107 children with moderate to severe AE, in which they showed that the great majority (97 out of 116 positive DBPCFC) developed eczema after exposure to the culprit food as part of an early and/or late reaction, in some cases combined with other symptoms. In both studies, cow's milk, egg and wheat accounted for the majority of the reactions. Finally, Breuer *et al*[33] performed a retrospective study in which the importance of foods for the induction of late eczematous reactions in children with AE was addressed. The severity of AE was determined according to SCORAD. An immediate reaction was defined as occurring within 6 hours upon the ingestion of the last dose of food and a late reaction as thereafter. A late eczema-

tous reaction was defined as a deterioration of eczema with an increase in 10 SCORAD points or more. Forty six percent of 106 DBPCFC performed in 64 young children with AE were positive, 57% of which with late eczematous reactions, either isolated (12%) or preceded by immediate reactions (45%). The highest proportion of children with isolated eczematous reactions occurred after challenge with wheat. Combined reactions most often occurred after challenge with egg, followed by cow's milk, wheat and soy.

Elimination of culprit foods from diet leads to improvement of food allergy-related atopic eczema

A number of interventional studies have focused on the utility of elimination diets in the treatment of AE (Table 3). In 2004, Fiocchi *et al*[34] systematically reviewed the existing evidence on dietary intervention in the management of AE. This review included 15 studies, 14 of which prospective, that differed in various aspects, namely study population, criteria for AE diagnosis, trial design, types of dietary intervention, length of observation period, sample size and out-

Table 3. Main elimination diet studies for established atopic eczema

Study	AE population	Intervention	Design	Result
Atherton 1978[36]	36 children age 2-8 Y	Egg & milk elimination	Double blind cross over	65% improved
Munkvard 1984[42]	33 adults age 16-25 Y	Elemental diet	Parallel, randomised, prospective, controlled	No benefit over normal diet
Cant 1986[37]	19 breastfed age < 6 M	Maternal egg & milk elimination	Double blind cross over	23% improved
Nield 1986[38]	40 patients	Egg & milk elimination	Double blind cross over	25% improved
Devlin 1991[114]	37 children	Elemental diet	Open exclusion	73% improved
Broberg 1992[115]	12 children age < 4 Y	Egg, wheat & milk elimination	Open exclusion	66% improved
Mabin 1995[44]	85 non breastfed children	Elemental diet	Parallel single blinded	No benefit over placebo
Isolauri 1995[39]	45 non breastfed children with CMA	eHF/aaF	Parallel, randomised, prospective	Improved in eHF & aaF
Majamaa 1997[116]	27 children < 16 M	Milk elimination ± probiotic	Parallel, randomised, prospective	Improved only with elimination diet+probiotic
Martino 1998[117]	16 children < 2 Y	Elemental diet	Open exclusion	Improved in all patients
Lever 1998[40]	62 children	Egg elimination	Randomised, controlled trial	Small improvement
Niggemann 2001[41]	73 infants < 9 M	eHF/aaF	Open, Randomised, controlled	Improved in eHF & aaF
Leung 2004[43]	15 children < 3 Y	aaF/placebo	Cross-over, randomised, prospective, controlled	No benefit of aaF

Abbreviations: Y – years; M – months; eHF – extensively hydrolysed formula; aaF – aminoacid formula.

come measurement. Such heterogeneity precluded meta-analysis methods; however, elimination of specific foods from the diet was efficacious in improving AE lesions in 13 of the included studies. This was particularly relevant in infants, patients with elevated serum IgE, sensitisation to multiple foods, severe forms of AE and/or established diagnosis of FA. Many of these studies had important limitations, including lack of blindness, selected population (observed in tertiary clinics, differing from the general population of patients with AE), short follow-up periods, high drop-out rates, lack of statistical power and concomitant interventions (e.g. pharmacological treatment, environmental control measures).

Recently, a Cochrane review[35] assessing the effects of dietary exclusions for the treatment of established AE was published. It included 9 randomised-controlled trials, involving a total of 421 participants. Six were studies of cow's milk and egg exclusions (3 cross-over studies[36-38] and 3 parallel studies[39-41]), 2 were studies of elementary diets[42,43] and one was a study of few foods diet[44]. According to the meta-analysis, no benefit of egg and milk free, elemental or few foods diets was seen in unselected patients with AE, possibly because the majority of these patients had no FA. However, an egg-free diet seemed beneficial in infants with suspected egg allergy and positive specific IgE to egg. In fact, in one of the included studies[40] with 62 infants aged from 11 to 17 months sensitised to egg (as detected by RAST), a significant improvement in body surface area affected by eczema and AE severity score was observed in the group where a 4-week egg exclusion diet was followed compared to the control group.

In a study by Isolauri *et al*[45] about the role of maternal dietary modification in established AE, one hundred exclusively breast-fed infants with AE were enrolled. The extent and severity of AE, allergic sensitisation, and the patients' growth and nutrition were assessed during and after cessation of breast-feeding. Strict elimination in mother's diet led to some improvement of symptoms. When breastfeeding was stopped and the infant was given an elemental formula, a significant improvement in AE and nutritional parameters were observed.

Studies in adults with severe AE are limited but have not shown a role for food allergy[46] or an amelioration in eczema symptoms with elimination diets[42]. A Japanese study[47] implicated foods in the exacerbation of AE lesions in 44% of an adult population, but these were uncommon food allergens (e.g. chocolate, coffee and glutinous rice) and specific IgE to those foods were mostly negative. In a German study[48], the majority (70%) of adult patients with AE were sensitised against pollen allergens and pollen-related food allergens, but relevant symptoms from sensitisation to these foods was not common (only 44% of the patients submitted to OFC showed a positive challenge, three quarters of whom developed isolated oral allergy syndrome). Analysing food allergens, sensitisation to hazelnuts, carrots, sesame, apple and celery were the most frequent. Sensitisation to the food allergens which play an important role in children, such as milk, wheat and egg, were rare in this study population. It is possible that some of these patients had allergy to these foods in the past as these food allergies are commonly outgrown as children grow older.

Food allergens are involved in the immunological mechanisms of atopic eczema

There are a considerable number of laboratory studies implicating food allergy in the IgE and non-IgE mediated mechanisms of AE, which further documents the close association between these two clinical entities.

The pattern of cytokine expression of lymphocytes infiltrating acute AE lesions is predominantly of the Th2 type, including IL-4, IL-5 and IL-13[49,50]. The Th2 cytokines are capable of upregulating high-affinity IgE receptors on skin antigen presenting cells[51], including Langerhans cells, which are very efficient at presenting antigens to T cells and inducing a Th2 response. This includes the production of IgE antibodies, the degranulation of mast cells and basophils and the influx and activation of eosinophils.

Patients with AE commonly have high serum total and specific IgE levels, including specific IgE to foods[52]. Sampson *et al*[53] determined the plasma histamine concentrations before and after DBPCFC (preceded by 10 days of elimination

diet) in patients with AE and suspected FA. Increase in plasma histamine level was observed only in the group of patients with positive DBPCFC. This study implicated mast cell and/or basophil mediators in cutaneous reactions to foods in patients with AE. Furthermore, Sampson *et al*[54] reported an increased spontaneous histamine release and production of histamine releasing factor in patients with FA and AE compared to patients with AE and no FA and to healthy controls. The spontaneous histamine release returned to normal levels when patients were on an appropriate elimination diet. The histamine releasing factor was found to activate basophils through surface-bound IgE. It could activate basophils from other food-allergic patients, but not from healthy controls.

Different studies support the role of eosinophils in the pathogenesis of FA-associated AE, especially in the late phase response of IgE-mediated hypersensitivity. Blood eosinophilia is a common feature in AE, but the accumulation of eosinophils in the skin is not always found in AE lesions. Leiferman *et al*[55] analysed skin biopsies by immunofluorescence for the presence of eosinophil-granule major basic protein and found an extensive dermal deposition of this protein in lesional biopsies but not in normal appearing skin of affected subjects. Suomalainen *et al*[56] studied 28 children with cow's milk allergy, 17 of whom with cutaneous and 11 with gastrointestinal manifestations. A cow's milk challenge was performed after a 4-week elimination diet. The serum level of eosinophil cationic protein (ECP) was measured before and after the challenge. An increase in serum ECP was observed only in patients with cutaneous manifestations upon ingestion of cow's milk. This suggests that the ingestion of a food in an allergic patient may lead to the activation of eosinophils that infiltrate the skin of patients with AE. Magnarin *et al*[57] further related the severity of AE with the number and extent of activation of the eosinophils in the skin.

Apart from the IgE-mediated mechanisms, cell-mediated hypersensitivity also takes part in FA in patients with AE. Several studies have implicated food-specific T cells in the skin inflammation of patients with AE. These cells have been isolated from active AE lesions[58-60] and peripheral blood in patients with FA and AE[59-61]. Conflicting data in the literature can be found about the *in vitro* T lymphocyte proliferative responses to specific foods in AE. On one hand, some studies[62,63] found that proliferative responses of peripheral blood mononuclear cells to the offending food allergen in patients with non-immediate FA were higher than in those with immediate FA or healthy controls and seemed to be food-specific in non-immediate reactions in patients with FA and AE. On the other hand, another study[60] found increased lymphocyte proliferative responses to the relevant foods in patients with immediate reactions. Hoffman *et al*[64] evaluated the utility of lymphocyte proliferation assays in the diagnosis of cow's milk allergy and concluded that they were neither diagnostic nor predictive of clinical reactivity in individual patients, as lymphocytes of many control subjects were highly responsive to milk allergens.

Summary: *Clinical studies have shown that in patients with FA-associated AE, elimination of the relevant food from the diet can lead to the improvement of the skin lesions and repeated exposure by oral food challenge can reproduce the skin symptoms. Laboratory studies have supported the role of implicated foods in the mechanisms of IgE-mediated and non-IgE-mediated hypersensitivity responsible for AE lesions.*

ROLE OF ATOPIC ECZEMA IN FOOD ALLERGY

Although our understanding of genetic susceptibility to AE has increased, it does not seem to be sufficient to explain the increasing prevalence of AE in the recent years. In this trend within such a short period of time, environmental factors may play an important role. However, primary defects of the skin may favour the intervention of environmental factors towards allergic sensitisation. A link between increased IgE production and the severity of AE has long been recognised[65], but a causal relationship remains to be established. A Th2-type immune response has been associated with the atopic status in patients with AE. However, not all patients with AE are allergic. In fact, AE[66] has been classified in allergic and non-allergic, the former being IgE or non-IgE mediated[67].

Skin barrier dysfunction

There are different arguments showing that one should focus on the skin not only as a target of atopy and allergic inflammation but also as an important site in the initiation of AE and the remaining atopic disorders[68]. Non-lesional skin of AE patients shows subtle epidermal abnormalities, depletion of lipids[69] (especially ceramides, which consolidate the stratum corneum) and of hydrophilic proteins[70] (e.g. filaggrin, which is a precursor of hydrophilic molecules important in moisturising the stratum corneum) and increase in transepidermal water loss[71], resulting in a global impairment of the skin barrier.

Genetic defects conferring epidermal barrier dysfunction have been associated with an increased prevalence of AE. An example is icthyosis vulgaris, an autossomal dominant disorder characterised by a defective expression of filaggrin in the epidermis[72]. Taïeb *et al*[73] suggested an explanation for the link between this structural defect and the immunological mechanisms in AE, based on the degradation of filaggrin yielding urocanic acid, which may act as an immunomodulator in the epidermis. More recently, Palmer *et al*[74] have described two variants of filaggrin defects as major predisposing factors for AE, suggesting that a primary epithelial barrier defect is the basis of AE. Null mutations in the filaggrin gene were associated with AE severity and persistence, concomitant asthma and asthma severity (but not with psoriasis, intrinsic eczema and asthma independent of eczema). The increased permeability of the epidermis to environmental allergens would facilitate its presentation to the skin immune cells and consequent allergic sensitisation in predisposed individuals.

Sensitisation to food allergens may occur through the skin

There is growing body of evidence showing that sensitisation to foods may occur through the skin, especially through inflamed skin. In a large prospective birth cohort study, Lack *et al*[75] showed an association between peanut allergy proved by DBPCFC and early onset of eczema and other oozing or crusting skin rashes. Low-dose repeated exposure to peanut protein in the form of arachis oil applied to infant's inflamed skin was associated with increased risk of peanut allergy at the age of 5[75]. Although the use of such oils is not widespread throughout the world, food allergens have been measured in the environment (in house dust[76], on furniture's surfaces and hands[77]) in quantities able to cause allergic sensitisation[78]. Such quantities of environmental food allergens may even be greater than common airborne allergens such as house dust mite[79]. Fox *et al*[16] in a questionnaire-based study showed that peanut consumption in the household of children with AE and peanut allergy was significantly greater than in the household of children with AE and egg allergy (who were not sensitised to peanut) and of non allergic controls, whilst significant differences in maternal peanut consumption during pregnancy or breastfeeding were not found. This data supports environmental, epicutaneous exposure to peanut as being the most likely route of sensitisation.

In murine studies, exposure of abraded skin mimicking eczema to food proteins led to food-specific IgE responses[80,81], as opposed to ingestion of high doses of food protein which promoted oral tolerance and prevented subsequent IgE sensitisation and T-cell proliferation[82]. In human subjects, food allergen specific T cells have been isolated from lesional skin in patients with eczema[58]. Abernathy-Carver *et al*[59] showed that after *in vitro* stimulation of T cells with casein, patients with cow's milk allergy and AE had a greater proportion of CLA+ T cells (cutaneous leucocyte antigen, a skin homing receptor) than those with cow's milk-induced enterocolitis, eosinophilic gastroenteritis or non-atopic healthy controls. In contrast, the proportion of L-selectin (receptor involved in the migration to the peripheral lymph nodes) expressing T cells were similar between the 3 groups, suggesting that homing receptor expression on food-specific T cells may determine the sites of involvement in allergic responses. More recently, Chan *et al*[83] showed that peanut allergic children exhibit higher proliferation of CLA+ compared to $\alpha 4\beta 7$+ (gut homing receptor) memory T cells *in vitro* after stimulation with peanut extract, as opposed to peanut tolerant

children. This supports the hypothesis that sensitisation to peanut occurs through skin while exposure via the gastrointestinal tract induces tolerance.

Summary: *AE is an inflammatory skin disease characterised by a loss of epidermal integrity. Disruption of the epidermal barrier could be a major route for allergic sensitisation, including to food allergens in the environment. Data from murine and laboratorial studies further support the concept that sensitisation to foods may occur through the skin.*

DIAGNOSIS OF FOOD ALLERGY-ASSOCIATED ATOPIC ECZEMA

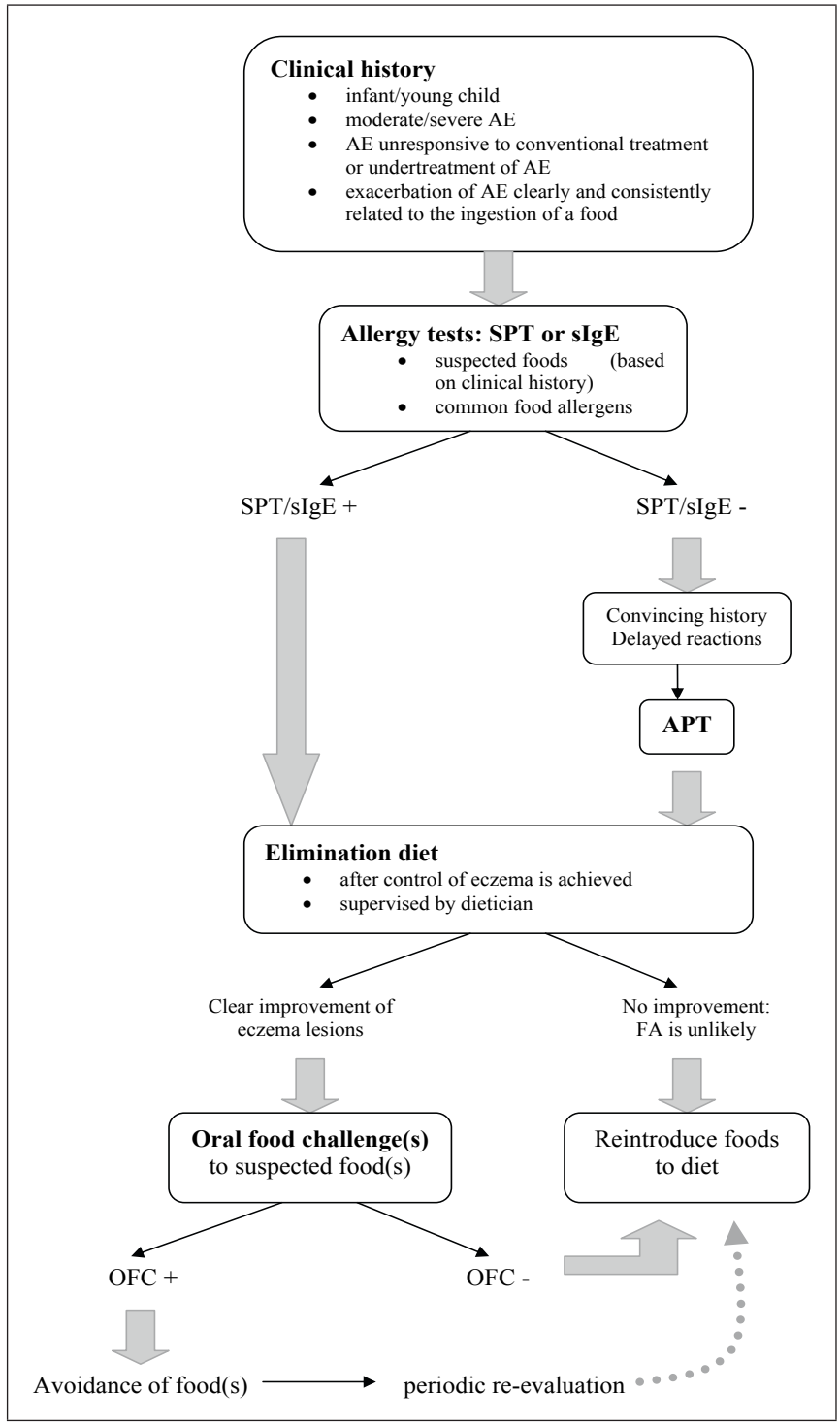
The diagnosis of FA-associated AE (i.e. children with both FA and AE, where food allergens account for eczema exacerbations) relies on a detailed clinical history and physical examination, allergy tests, elimination diets and oral food challenges, as appropriate (Figure 2). However, there are several factors complicating this process, which have to be considered so that an accurate diagnosis and an adequate diet can be established. Firstly, AE is characterised by a waxing and waning course and several environmental factors other than food allergens may account for the exacerbation of symptoms, obscuring the effect of the ingestion of specific foods or changes in diet. Secondly, the reaction after the ingestion of an implicated food may have different timelines (i.e. immediate, late or delayed reactions) and immediate reactions may even be downregulated by repeated exposure to the allergen. Thirdly, patients with AE have a propensity to produce IgE antibodies to various allergens, which does not allow a diagnosis of food allergy to be made based only on allergy test results alone as allergic sensitisation and allergic disease are two different concepts. Although the cut-off levels corresponding to a 95% positive predictive value have been validated in children with AE in tertiary clinics, these children may have clinically irrelevant allergic sensitisation to multiple foods. Conversely, children who are SPT or specific IgE negative may develop delayed eczematous reactions to foods on OFC[32]. Therefore, the cornerstone of an accurate diagnosis of AE is a detailed and careful clinical history, which allows judicious interpretation of diagnostic tests and design of patient-tailored elimination diet and OFC. Given that the diagnosis of FA in children with AE is complex and may lead to dietary modifications, which have implications in nutrition and growth, it is extremely important to diagnose it correctly.

Clinical history

The clinical history should include a general medical history and specific aspects addressing possible food allergy. Regarding AE, it is especially important to confirm the diagnosis, determine its age of onset, severity and response to treatment. Non-response to treatment should be distinguished from undertreatment and/or non-adherence and topical therapy should be optimized.

The FA-related history should start with a detailed description of the reaction(s) after contact and/or ingestion to the implicated food(s), including quantity and processing of the suspected food(s), symptoms, timing between the ingestion of the food and the development of symptoms and consistency of the reactions. Three patterns of skin reaction to food may develop in patients with AE[84]: immediate reactions which are likely to be IgE-mediated (e.g. urticaria, angioedema); pruritus and/or erythema in the predilection sites for AE within about 2 hours after food ingestion (which may also be IgE-mediated but may lead to an exacerbation of the eczema); and, finally, delayed reactions with AE exacerbation, that usually occur after 6 to 48 hours, with or without a previous immediate reaction, and may be mediated by a non-IgE mechanism or a late-phase reaction of IgE mediated hypersensitivity. The report of skin reactions on contact of the food with the skin is common[85]; however, it may not correspond to an immunologically mediated reaction but to an irritant effect of the food on abraded sensitive skin.

The clinical history should also include a dietary history, including patient's current diet (breast milk or formula in case of an infant, which foods and quantity of foods are tolerated, asking specifically about each food group), breastfeeding, wean-



Abbreviations: AE – atopic eczema; FA – food allergy; SPT – skin prick test; sIgE – serum specific IgE; APT – atopy patch test; OFC – oral food challenge.

Figure 2. Diagnosis strategy in food allergy-associated atopic eczema

ing and eventual reactions at time of weaning. For breast-fed infants, a maternal dietary history should also be obtained. Although any food is theoretically capable of causing an allergic reaction, a limited number of foods accounts for the great majority of them[17,20,86]. The most common implicated foods in infants and children are cow's milk, egg, soy, wheat, peanut, tree nuts, fish and shellfish; and in older children and adults peanut, tree nuts, fish, shellfish, fruits and vegetables. In children with FA and AE, egg, cow's milk, peanut, wheat and soy are the commonly implicated foods[17]. The prevalence of each food in food allergy varies with age and geographical location. Special attention should be paid to foods that may be ingested at the same time or potentially contaminated and hidden allergen sources. Dietary diaries completed at home may be useful when taking a history, as well as labels from suspected packaged foods. Associated activities may play a role in the development of immediate allergic symptoms (e.g. exercise) and other factors present at the time of reaction may be important in the induction of skin symptoms (e.g. heat), in the particular case of AE. It is also important to ask about symptoms of gut dysmotility (e.g. colic, gastroesophageal reflux, diarrhoea, constipation) and assess weight gain and thriving.

During physical examination, the physician should seek for other features of the atopic diathesis, which brings the diagnosis of allergic AE more likely and may draw attention to associated atopic conditions, which also require appropriate management.

After completing the clinical history, the physician should determine whether it suggests food-induced AE and which is the most likely mechanism involved. FA in children with AE is more likely when a history of exacerbation of AE is clearly related to exposure to a specific food and in infants and young children (especially infants younger than 6 months) with moderate or severe uncontrolled AE and fine steroid usage, in some cases also presenting with gut dysmotility or failure to thrive.

Reported food allergy is more common than true FA, with only about 40% of the histories being confirmed by DBPCFC. Therefore, the following step in the evaluation of FA in AE should be the performance of allergy tests and OFC. Allergy tests are much more useful in IgE-mediated than in non-IgE mediated FA, which cannot be ruled out based only on negative allergy tests and demand elimination diets and specially designed OFC to confirm or exclude the diagnosis.

Allergy tests

In order to detect food-specific IgE, SPT or *in vitro* tests (RAST or ImmunoCAP®) can be performed. However, these tests determine allergic sensitisation and not clinical allergy. A significant proportion of atopic individuals, especially those with severe AE, may have high levels of total serum IgE[52] as well as specific IgE to multiple food allergens[87]. In an Australian study, 91.5% of breastfed infants with moderate to severe AE had positive SPT to one or more foods[88], 80% of which were reactive to egg. However, allergic sensitisation may occur without symptomatic food allergy[21]. When interpreting allergy test results, the clinical relevance of a given sensitisation should be determined.

The first step when performing SPT and/or serum specific IgE is to select the food allergens to be tested. These should include suspected foods identified on clinical history and common food allergens considering patient's age and geographical location.

SPT and serum specific IgE have high negative predictive value (>95%) but low positive predictive value (only about 30 to 40% of patients with food specific IgE antibodies actually develop clinical symptoms after the ingestion of the food[89]). Therefore, a negative test virtually rules out IgE-mediated allergy to a specific food, but a positive test is not enough to confirm it. However, the higher the weal size on SPT and the higher the concentration of serum food-specific IgE antibodies the more likely it is the clinical allergy after the ingestion of a food[86,89]. In this view, cut-off values were determined for SPT and specific IgE for common foods as a strategy to improve the diagnostic accuracy of these tests[90-93] (Table 4). The sensitivity of these diagnostic decision points was shown to be limited, thus these should be used to confirm food allergy and not to exclude it. This means that patients with a specific IgE level above the 95% positive predictive value for one of

Table 4. Cut-offs for ≥ 95% positive predictive value of SPT[90,118] and serum specific IgE[91,93]

Foods	SPT wheal diameter (mm)	sIgE (U/ml)
Milk	8	32
Infants ≤ 2yrs	6	5
Egg	7	6
Infants ≤ 2yrs	5	2
Peanut	8	15
Infants ≤ 2yrs	4	ND
Tree Nuts	ND	15
Fish	ND	20

Abbreviations: SPT – skin prick test; sIgE – serum specific IgE; ND – not determined.

those foods would be extremely likely to react if they ingested the food and thus did not need to undergo an OFC to establish the diagnosis of food allergy. However, patients with a specific IgE level below the 95% positive predictive value and above the 95% negative predictive value needed an OFC to confirm (or exclude) clinical allergy. Patients with a specific IgE level below the 95% negative predictive value were unlikely to react after the ingestion of the food and it might be (re)introduced in the patient's diet, unless there is a convincing history of allergic reaction, in which case they should undergo an OFC. These cut-off values allowed the reduction of the number of OFC by 40 to 50%. However, as these cut-offs rely on predictive values, they depend on the prevalence of food allergy in the studied population and may not be able to predict clinical reactivity in different populations, probably with lower prevalence of atopy and food allergy.

When performing allergy testing, especially SPT, allergen extracts from a certain source are being used, which may not be representative of the allergenic food as it naturally occurs. Commercial allergen extracts of certain foods, such as fruits and vegetables, are not of good-quality as some allergens are easily degraded and are not present in the solutions used. Therefore, SPT with fresh foods (i.e. prick to prick testing) should be performed, with foods in both raw and cooked forms. This is especially useful in the presence of a convincing clinical history and negative SPT.

In the interpretation on SPT and specific IgE results, special attention should be drawn to cross-reactive food allergens (e.g. legumes, cereal grains, egg and chicken meat, cow's milk and beef). Although positive allergy tests are common to different elements of the same family (i.e. immunologic cross reactivity), not all patients develop symptoms to those foods. Avoidance of all foods within a family of allergens is not advisable, especially in multisensitised patients. Exceptions to this general recommendation may be tree nuts, fish and shellfish, due to the high risk of cross-contamination and severity and persistence of the reactions commonly elicited by these foods, but decisions have to be made depending on each particular case.

While immediate food allergy can be identified more easily with a combination of the clinical history and SPT and/or specific IgE results, delayed reactions present with more diagnostic difficulties. Atopy patch test (APT) was shown to have a good predictive value for late phase clinical reactions during DBPCFC[31,94]; and therefore, could be useful in the diagnosis of FA in children with AE[95]. Isolauri *et al*[31] performed a study with cow's milk allergic children with AE in which 67% of children with immediate reactions on oral cow's milk challenge had positive SPT and negative APT; on the contrary, 89% of the ones with delayed-onset reactions during OFC had positive patch tests and negative SPT. The close macroscopic and histological similarities between positive APT sites and AE lesions support the use of APT in the diagnosis of FA in children with AE. Studies showing that positive APT are characterised by allergen-specific T-cell infiltration[96] and correlate with clinical late phase reactions in OFC[94] further supports its use.

Although APT seems not to add much predictive value to SPT and specific IgE in routine FA diagnosis[97], it seems to be useful in selected populations with AE and suspected FA. Niggemann *et al*[94] enrolled 75 children with sus-

pected FA, 92% of whom with AE, and performed DBPCFC, SPT, specific IgE and APT to different foods. Immediate reactions during DBPCFC were associated with positive SPT and specific IgE, while for late phase reactions the sensitivity and specificity of SPT were 58% and 70%, of specific IgE were 71% and 29% and of APT were 76% and 95%. Roehr *et al*[98] showed that APT was the best single predictive test for evaluating food allergy in a population of children with AE and FA. Combination of APT results with serum specific IgE level improved the positive predictive value of APT and reduced the need for OFC in these children. For specific food allergies, APT was found to have positive predictive value of 70% for cow's milk allergy, 94% for egg and wheat allergies. Nevertheless, APT presents a few limitations for its routine use in clinical practice[97,99] as it is technically demanding, time consuming and unstandardized for the majority of food allergens[100]. Recommendations for its use have been published[95,101].

Elimination diets and oral food challenges

In certain circumstances, an elimination diet followed by oral food challenge(s) is the only way to establish the diagnosis of FA in patients with AE. For example, when the results of allergy tests together with the clinical history are difficult to interpret, children are sensitised to multiple foods and/or the clinical expression of FA is a delayed exacerbation of the eczema.

First of all, it is crucial to control the eczema with general and pharmacological measures as much as possible, so that worsening or improvement of the skin lesions with dietary modification can be clearly noted. Gaining control of the eczema before starting an elimination diet also allows the parents to evaluate if the foods actually play a role in the exacerbation of AE. Thompson *et al*[102] during an open trial of topical tacrolimus observed a decrease in parental food allergy concern during good control of their child's AE. They performed a questionnaire-based study[102] to confirm that successful stable treatment of AE reduces perceived food reactions and redirects parents' attention to topical skin care as the primary treatment of AE.

When FA is likely, a strict avoidance of the food(s) suspected of being responsible for food-induced AE should be implemented. In the case of general suspicion of food allergy, an oligo-allergenic diet may be recommended. In the most extreme situation, when avoidance of a specific food or an oligoantigen diet has failed, an elemental diet should be implemented. In breastfed infants when restriction in the mother's diet has failed or in formula-fed infants, an aminoacid formula should be preferred. All elimination diets should be supervised by a specialised dietician so that a balanced diet can be maintained and nutritional deficiencies anticipated and avoided.

In patients with AE, an elimination diet should last for 4 to 6 weeks in order to see a change in skin lesions. If the skin symptoms persist after a strict elimination diet, it is unlikely that the foods account for the patients AE and the foods should be reintroduced. However, if there is an improvement with appropriate dietary elimination of the suspected foods, OFC should be performed to confirm clinical reactivity. Relying food allergy diagnosis only on the history, allergy tests and elimination diets may lead to misdiagnosis in up to 50% of cases[103].

OFC in patients with AE and suspected FA should follow the general recommendations for such procedures[104,105], adjusted to special features of this condition[106]. As patients with AE may develop immediate reactions to foods in organs other than the skin, physician supervision and rescue facilities should be available. Challenges to different foods may be needed when there is more than one suspected food, previously eliminated from the diet. In this case, the order of foods during challenge depend on the results of allergy tests, nutritional requirements and the dietary habits of the patient and his/her family. It is crucial to gain control of the eczema before OFC. Apart from general baseline assessment, the patient's skin should be carefully observed before starting the challenge. Clinical monitoring during OFC should be standardised (e.g. using symptom scores). Ideally, DBPCFC should be preferred over single-blind or open food challenge. This is especially important in the case of AE where reactions may be more difficult to interpret. However, if necessary, an open challenge may be performed in

the first instance followed by a DBPCFC in the case of a positive outcome. A special design for DBPCFC should be used, with an extended period of observation. For instance, on day 1 increasing doses of placebo could be administered followed by a day of observation and on day 3 graded doses of the first food would be given followed by a day of observation and so on. If the history indicates that the suspected food has to be ingested for a longer period of time for a skin reaction to occur, the design of OFC should be adjusted to evaluate the history. For the definition of a late phase reaction, time should be counted from the highest dose and not from the first one. As methodological problems raise difficulties in the performance of OFC in children with AE and suspected FA, especially in case of delayed eczematous reactions, these procedures should only be performed in specialised centres by experienced staff.

A positive reaction after the ingestion of the food and negative after placebo allows a diagnosis of allergy to that food to be made. Positive reactions to both a specific food and placebo demand repeating the OFC. A negative reaction to a food on DBPCFC should be followed by open feeding of age-appropriate meal-size portions of the food. Then, a diagnosis of allergy to that food is excluded and the food should be immediately included in the patient's diet.

Summary: *The diagnosis of FA in patients with AE is based on a detailed clinical history, SPT, specific IgE, APT, elimination diets and OFC, as appropriate. Even in patients who have negative SPT or specific IgE to the suspected food, AE exacerbations may be caused by that food. An accurate diagnosis is crucial to detect the culprit food(s) and either improve the skin lesions or avoid unnecessary dietary restrictions. Every patient with AE should be tested for atopy, so that prognosis, disease association, severity and response to treatment can be determined.*

DIETARY MANAGEMENT

Apart from the medical management of AE (patient education, emollients, topical corticosteroids, topical calcineurin inhibitors and antibiotics), the cornerstone of the treatment of FA-associated AE is the avoidance of the offending food(s). In breastfed infants, restriction of the identified allergens should be implemented in the mother's diet under supervision of a specialised dietician to anticipate nutritional deficiencies (e.g. calcium deficiency in case of cow's milk free diet). Complete elimination of a specific food is not an easy task and patient's education is very important. Patients should be informed that the food protein is the ingredient to be eliminated and not the sugar or the fat. Patients and parents should be instructed to read the ingredient labels and be able to recognise different words for the presence of food proteins. Dietary modification should be supervised by a specialised dietician, especially when multiple foods are being excluded from the diet. On one hand incomplete allergen avoidance may lead to ongoing chronic symptoms (a flare of AE during a period of improvement is more likely due to inadvertent ingestion of an hidden food allergen rather than a reaction to a new food); on the other hand, avoidance of essential foods may result in impairment of growth and development, deficiency of specific nutrients (e.g. avoidance of cow's milk significantly reduces calcium and iron intake) and appropriate supplementation may be required.

Every patient should be also given an emergency treatment plan stating the food(s) to be avoided and including the medications to be taken in case of an accidental ingestion of the identified food allergen(s). Depending on the risk factors and previous allergic reactions, this may include injectable epinephrine, oral anti-histamine, inhaled short-acting β2-agonists and/or oral corticosteroids. Patients and caregivers should be informed about the indications and mode of administration of each medication and instructed to seek medical care in case of an allergic reaction.

An elimination diet should be maintained for the shortest period of time possible. Patients should be followed up over time for the assessment of growth, nutrition and eventual acquisition of tolerance to each of the identified food allergens. Once tolerance is acquired, the food should be reintroduced in the patient's diet.

Most children outgrow their allergies to cow's milk, egg, wheat and soy[107] and related AE. Although recent studies on the natural history of IgE-mediated cow's milk allergy, for example, show less optimistic results[108], children continue to progressively achieve tolerance into adolescence and even adulthood. There are, however, allergies to specific foods that tend to persist into adulthood (e.g. allergies to peanut, tree nuts, fish and shellfish). Sampson *et al*[30] have described a loss of clinical reactivity to foods of 26% after the first year and of 9% after 2 years in patients with AE adhering to an elimination diet. In this study, total IgE and SPT were not useful for predicting loss of symptomatic FA. Although the specific IgE level and the degree of decrease over time has been related to the acquisition of tolerance to certain foods[108,109], this has not always been advocated for children with FA and AE[110], who may maintain high levels of specific IgE or large wheal diameters on SPT to foods they are able to tolerate. Therefore, it is necessary to re-challenge these patients in order to assess the development of tolerance and reintroduce the implicated foods in the patient's diet as soon as they are no longer an issue. However, this does not exclude the importance of repeating allergy tests during follow-up – e.g. children with FA-associated AE who do present with negative allergy tests at the time of diagnosis should be re-tested before assessment with OFC, under medical supervision, in order to assess the possible development of immediate-type FA during allergen avoidance, which has been reported[111].

The decision of when to challenge depends on the natural history of the allergy to a specific food, the age of the patient and how the outcome will affect the family. It is important that once tolerance is demonstrated, the food is introduced into the child's regular diet as this seems to be required to maintain tolerance[112]. Although FA and AE tend to resolve in children, in some they may persist. Infants and children with FA and AE are also at risk of developing further allergic sensitisations and respiratory allergies in the future[13,113].

Summary: *Management of FA in children with AE includes medical treatment of the eczema lesions and avoidance of the offending food(s). Elimination diets should be based on an exact diagnosis of food allergy to a specific food and should be supervised by a specialised dietician. An appropriate written treatment plan should also be issued. Patient's follow up over time should aim at evaluating acquisition of tolerance (as well as nutritional status, growth and development in children) and once tolerance is achieved, the food should be reintroduced in the patient's diet.*

CONCLUSION

FA and AE are closely related and share pathological mechanisms. Clinical and laboratory studies have further defined the relationship between FA and AE. In clinical practice, in a subset of children with AE, specific food(s) account for exacerbation of cutaneous symptoms and commonly also for immediate allergic reactions in other organs and evaluation for FA should be performed. Special attention should be drawn to eventual unnecessary dietary restrictions, suboptimal eczema treatment and development of immediate allergy to the avoided foods in these patients.

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