Atopic Dermatitis and Food Allergy: An Associated Genetic Burden

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Abstract

Background: The association with food allergy (FA) in children with atopic dermatitis (AD) confronts the allergists with one of their most genetic challenges. The fluctuating clinical course of the diseases and the large variety of the environmental triggering factors make the identification of the offending food(s) rather difficult. Since foods are common triggering factors of AD in infancy and in childhood, it would seem obvious that elimination diets should be useful in the identification of the offending food(s) in these patients.

Objective: Historical information referred by parents and elimination diets are rarely helpful for the identification of the offending foods and only double-blind placebo-controlled oral food challenges (DBPCOFC) are useful for the diagnosis. The diagnosis of FA in infancy and in childhood is a challenge both for the pediatrician and allergist because it can be easily accomplished only when there is a relation between the ingestion of the offending food(s) and the onset of the symptoms, and when it can be demonstrated that these symptoms are the consequence of an immunological reaction. However, the underlying immunologic mechanisms may be difficult to document, and the only immunologic mechanism easily to prove in current practice is the IgE-mediated one.

Conclusion: In this article we analyze the first steps in achieving the diagnosis of FA. The manifestations due to FA, including cow’s milk (CM) allergy (CMA), are common also to other diseases, and in addition no reliable laboratory tests are available, therefore the diagnosis should be done on a proven demonstration that the symptoms are correlated to the ingestion of the specific food, and that the diagnostic tests indicate an immunologic pathogenesis.

Keywords: Food allergy; Atopic dermatitis; Cow milk allergy; Cow milk substitutes; Home-made; Meat-based formulas (Rezza’s diet); Cow milk protein hydrolysate formulas (HFs); Diagnosis; Challenge test; Bovine spongiform encephalopathy; Mad cow disease; Tacrolimus

Introduction

Recent surveys indicate a significant increase in the prevalence of AD and estimations of prevalence of AD in childhood vary between 8 and 14 % [1]. In children of atopic parents the estimated prevalence of AD in the first year of life is about 50% [2]. CM, chicken eggs and peanuts are the most common childhood allergens, several types of cereal grains and prollines (proteins contained in pollen) can also induce allergic reactions. In addition to foods, the factors that may significantly affect AD outcome and predictive unfavorable factors are late onset of the disease, atypical or widespread skin lesions, persisting FA [3]. Prevalence of respiratory allergy in children with AD has been estimated about 60% [3]. Emotional stress, contact irritants, skin infections and overheating are important contributory factors to AD once established. Recently, groups of investigators suggest that environmental allergens such as house dust mites and pollens can trigger AD [4].

The Role Of Food Allergy In AD

The role of FA in AD was first suggested in 1936 [5]. The authors reported that CM feeding early in life was a significant contributory factor in AD and the prevalence of AD was seven times higher in CM-fed babies than in breast-fed babies [5]. In 1955 [6] it was reported that skin rashes and urticaria frequently occurred in babies up to three months of age administered egg white, and the prevalence of such disorders was significantly reduced when egg white was given after six months of life. Data on the role of FA in AD are supplied by the finding of food-induced contact urticaria, frequently occurring in children with AD. In addition, children with AD may experience a large spectrum of manifestations associated with FA, some of which are immediate and severe (angioedema, laryngospasm) while others have a more insidious and chronic clinical course, cutaneous (urticaria, angioedema, pruritus, erythematosus macular rashes, AD), respiratory (coughing, wheezing, profuse nasal rhinorrhea, sneezing, and laryngeal edema), and gastrointestinal symptoms (nausea, cramping, vomiting, flatulence, and diarrhea) and even anaphylactic shock after challenge test with the offending food (Table 1). Another indirect evidence of the role of FA in AD is the significant improvement of the skin lesions after institution of a suitable elimination diet. An elegant cross-over double-blind study [7] demonstrated a marked improvement of AD in children receiving an egg- and CM-free diet (soy protein formula - SPF - as CM substitute). It was noted that 14/20 children on this diet showed a significant improvement of the skin lesions, whereas only one on an egg- and CM-free diet had a favourable response. It was subsequently shown that babies who received solid foods in the first 4 months of life had a significantly increased risk of AD compared with babies not receiving solid foods in their diet. Furthermore, the rates of AD increased in nearly direct proportion to the number of different types of solid foods given to the babies in the first 4 months of life; babies fed 5 or more different solid foods had over twice the risk of eczema compared to children receiving no solid food [8].

The role played by the type of feeding early in life and the onset of AD is provided by the promising results obtained in high-risk babies with preventative dietary manipulations. A significant reduction in both the prevalence and severity of AD was shown by several studies recommending prolonged breastfeeding supplemented by extensively hydrolysed formulas (HFs) or SCFs [9,10].

The influence of early type of feeding on the onset of AD has been recently confirmed by sensitization to foods occurring more commonly early in life, however occasionally it may even occur prenatally. CM appears to be the most common offending food both in gastrointestinal (vomiting, diarrhea, etc) and in cutaneous manifestations (urticaria and AD). Specific IgE to foods and positive challenge test to a number of food allergens are frequently present in children with such disorders. FA and AD may negatively interfere with the child’s life and his physical and physiological development. Prevention should be therefore the early mainstay of each intervention. According to previous and recent studies, prevention of atopic diseases in genetically predisposed newborn babies, is not only worthwhile but also necessary. We always should investigate whether also the parents are allergic to foods [11].

The role of foods in AD is suggested to be more relevant in infants and in preschool children. The majority of children (75%) develop AD within

Table 1: Clinical manifestations of food allergy

| Skin: | urticaria, atopic dermatitis |
| Gastrointestinal tract: | Food-induced enterocolitis and colitis, Malabsorption syndromes (celiac disease) allergic eosinophilic Gastroenteritis (with gastroesophageal reflux) |
| Respiratory: | allergic rhinitis, asthma |
| Anaphylaxis: combination of the above symptoms |
the first year of life when the food antigenic load is prominent, especially in bottle-fed babies. Skin prick test (SPT) positive responses to foods are significantly higher in infants with AD compared to children with asthma. IgE antibodies to a great variety of foods are frequently detected in infants and in preschool children with AD [12]. In the last decades, DBPCFCF have conclusively demonstrated the role of FA in children with AD [13]. In addition, it was shown that almost 50% of children with AD may have food hypersensitivity. Eggs, peanuts, CM, wheat, fish and soybeans accounted for 90% of the positive reactions [13]. Employing two foods for challenges, a similar rate of positive reactions was obtained [14]. Children with AD are frequently reported to be allergic to a wide variety of foods, a deduction endorsed by the wide number of positive SPTs and RAST tests to foods found in children with AD. Even though children eat a great assortment of foods, CM, eggs and wheat are the most common foods consumed in the breast diet accounted for more than 95% of the positive responses. These data should be taken into account to eliminate the nutritional problems of too restrictive a diet potentially leading to malnutrition. Patients and parents should be provided with educational materials and instructed how to detect potential sources of hidden food allergens by appropriately reading food labels.

In conclusion, food hypersensitivity is an important triggering factor in almost 50% of the children with AD and the most common offending foods are CM and egg.

Pathophysiology

FA should be immunologically mediated, and this fundamentally correct concept has been too easily weakened by ignoring the prerequisite, at a point that FA has become a term commonly used to embrace all forms of adverse reactions. This has been favored and substantiated by the constellation of symptoms and the multiplicity of syndromes vaguely attributed to FA, and by the lack of a single laboratory test, at the same time, cheap, applicable and reliable for all clinical and immunological reactions. Faced with these problems, allergists have at length debated whether the most suitable denomination was FA or food (hyper) sensitivity. However, when the pathogenesis is uncertain or not immunologic, the term Food Intolerance (FI) should be used.

The ingestion of offending food(s) has been suggested that could lead to release of the mediators as a consequence of an IgE reaction, and high levels of serum histamine have been shown in children with AD after a positive DBPCFCF response [15]; but histamine release only (at the gastrointestinal and/or skin level) cannot completely explain the histology of the eczematous lesion. An important role is played by the late phase of IgE-mediated hypersensitivity, and evidence is accumulating that eosinophils actively participate in late phase-allergic reactions in different tissues, including the skin. When the ingested food antigen comes in contact with the skin mast cells, histamine and other chemotactants are released into local tissue. IgE molecules generate an inflammatory response through mechanisms other than direct mast cell activation. Consequently, neutrophils and eosinophils infiltrate the skin, thus contributing to the skin pathologic by releasing cationic proteins and various pro-inflammatory mediators. Eosinophils is frequently associated to AD, and generally its degree correlates with the severity of the disease also due to critical adhesion molecules for infiltration of T lymphocytes and eosinophils [16]. Although the pathophysiology of AD is not fully understood, there is evidence that eosinophils may play an important role in this process. Recent studies indicate a role for eosinophil disruption and degranulation in inducing tissue destruction. Several potent, toxic and cationic proteins have been described in the eosinophil granules. These include major protein (MBP), eosinophil-derived neurotoxin (EDN), eosinophil cationic protein (ECP) and eosinophil peroxidase (EPO).

It has been shown that some of these cationic proteins are elevated in the peripheral blood of patients with AD [16]. There is also evidence for eosinophil disruption and degranulation in the affected skin [17]. Finally, an active participation of eosinophils in patch-test reactions to inhalant allergens has been shown in patients with AD [18]. Eosinophils are not only active in mediating allergic inflammation but also interact in cellular networks with antigen-presenting cells, mast cells, and T lymphocytes. These other cells influence eosinophil maturation, mobilization, tissue localization and activation. In agreement with other authors, we found elevated serum levels of ECP in children with AD. It seems likely that elevated ECP serum levels in patients with AD may reflect the activation of eosinophils in the skin. It has been reported that in vitro ECP can induce an increased histamine release [19] and can suppress T-lymphocyte function via non-toxic mechanisms [20]. It is therefore tempting to speculate that ECP, besides having noxious effects for the skin, may contribute to the profound immunologic abnormalities described in patients with AD.

The detection of elevated ECP levels in the serum of AD patients may be an indirect measure of the pathological process taking place in the skin [21]. Thus, measurement of ECP might represent a noninvasive tool to assess the activity of AD in relation to eosinophil involvement in this condition.

Additional factors potentially involved in the eosinophil degranulation are platelet-activating factor (PAF) and cytokines interleukin (IL) IL-3, IL-5 and GM-CSF. An aggravating factor is the demonstration in AD and food-sensitive patients of histamine releasing factors (HRF) produced by peripheral blood mononuclear cells (PBMC) as a consequence of continuous food challenge. Children with AD and FA have high spontaneous basophil histamine release in vitro when compared with normal controls or AD patients without FA. These HRF are able to promote a continuous histamine release from mast cells and basophils [22]. It has been shown that spontaneous basophil histamine release (SBHR) is high in children with food induced AD while they are not on an restricted diet but it is close to normal when these children are on an elimination diet [22]. When these patients have adopted a food elimination diet for approximately 1 year, SBHR and HRF production fell to baseline levels and correlated clinically to a decrease in cutaneous hyper-reactivity. SBHR correlates to the HRF production from PBMCs and HRF may activate or decrease the activation threshold of both basophils and mast cells and could explain the high SBHR described in patients with AD. Basophils from non-atopic individuals were stripped of all IgE molecules and sensitized with IgE from FA patients. This rendered the "normal" basophils capable of secreting histamine in response to HRF [22].

It is noteworthy to stress that the mediators and ILs that can be released by various mechanisms induce itching, the main symptom of AD; this provokes scratching which, in turn, produces the skin lesions. However, lesions have been found in infants less than 2 months of age, before the appearance of coordinated scratching.

Diagnosis Of Food Allergy In AD

As with all medical disorders, the first step in the diagnostic approach to children with a suspected adverse food reaction to achieve the diagnosis of FA is a thorough history which may provide precise information to support or to rule out FA (Table 2). Unfortunately the clinical history is only occasionally useful and more frequently and especially in AD it does not provide valuable information. Based on this information additional laboratory studies may be warranted [23] (Table 3). The final diagnosis should be done with the challenge test. Many parents of very young children frequently have wrong feelings that foods trigger symptoms in their children. In the majority of these cases the association between the ingestion of the culprit food and the appearance of the symptoms is a coincidence. In such cases there is no need for a DBPCFCF, the reintroduction of the incriminated food, into the diet when the symptoms disappear, will convince the parents that the food can be well tolerated. However, the DBPCFCF is the gold standard for the diagnosis of FA [13].

Food challenge testing is far from meeting a unanimous consensus. The protocol is best conducted as follows: 1) The procedure is not risk-free and severe reactions may occur: challenge should be done in a clinical setting

1. Food suspected to have provoked the reaction
2. Quantity of the food ingested
3. Length of time between ingestion and development of symptoms
4. Description of the symptoms provoked
5. Similar symptoms developed on other occasions when the food was eaten
6. Other factors (i.e. exercise) necessary
7. Length of time since the last reaction

Table 2: Points to cover in the medical history

- Prick skin tests (PST)
- Food test for specific IgE (RAST)
- Oral challenges
- Elimination diet
- Double blind placebo-controlled food challenge (DBPCFCF)

Table 3: Useful diagnostic tests for food allergies
under constant supervision and with emergency equipment at hand for the possible onset of anaphylaxis, even in patients with no previous history of severe reaction. 2) Challenge must be avoided when the offending food is suspected of having caused previous systemic anaphylaxis in children with strongly positive skin tests and/or RAST related to clinical manifestations. 3) In infants with chronic diarrhea the test should be postponed until a clinical improvement is achieved and the children thrive normally. 4) A strongly positive challenge validates the diagnosis, therefore it is not necessary to repeat it as suggested in the past. 5) Symptoms usually manifest themselves within minutes/hours, however delayed-onset symptoms are frequent (colitis, AD). 6) There is no unanimous consensus about the doses to be administered, therefore it is advisable to start with little quantities of food to be gradually increased according to the response. 7) DBPCOCF testing is a necessary procedure. In children with objective symptoms such as diarrhea, urticaria, or angioedema, DBPCOCF is not strictly necessary for the diagnosis in clinical practice [14]. In any case, equipment for the management of anaphylaxis should be at hand.

An appropriate elimination diet should be given before the challenge up to four weeks in order to obtain the disappearance of the symptoms. A “diagnostic” oligoantigenic elimination diet should be given, since there are so far scarce laboratory tests for the diagnosis of FA (Table 3). Elimination diets obviate the need for careful clinical assessment; they can be adapted to the suspected sensitivities of the single patient. We use with good results a home-made meat diet as suggested by Rezza (Table 4). The formula is prepared as follows: fresh or frozen lean lamb’s meat (free from fat and tendons) is cut into small pieces, boiled and minced, then mixed with the other components of the diet. This formula is nutritionally adequate, has a pleasant taste, and is cheap. Once clinical improvement is achieved, wheat and saccharose are reintroduced into the diet, then various foods in sequence, with the obvious exception of CM. This diet provides 740 to 900 calories per liter and the distribution of nutrients and the energy provided by this diet are in agreement with the European Society of Pediatric Gastroenterology and Nutrition guidelines on infant nutrition. Among the advantages of this diet is the possibility of adapting it to the individual patient; that is, vegetables, fruit and meat, wheat flour and other nutrients can be added to the diet according to the age and weight of the child, and the doctor’s judgment.

Although diagnostic elimination diets are considered the most suitable procedure to detect offending foods, several factors may contribute to the lack of reliability of elimination diets in AD due to FA, since small quantities of triggering allergens may be heedlessly or inadvertently ingested by, or may reach FA children [24]. Cross-reactions may sometimes occur between closely related foods (eggs of different birds such as chicken, turkey, duck, and goose, milk of various species such as CM and goat milk, veal meat and CM, chicken meat and egg) (Tables 5 and 6). Beef meat is prohibited in these children, due to cross-reactions with CM, and because of bovine spongiform encephalopathy and mad cow disease. Cross-reactions also may occur between CM proteins and CM proteins HFs, especially partially hydrolyzed [25-27].

| Lamb meat           | 100g  |
| Olive oil           | 40g   |
| Rice flour          | 70g   |
| Table salt          | 2g    |
| Water until 1 liter |       |
| Calcium             | 500mg |
| Vitamins as needed  |       |

Table 4: Composition of Rezza’s Diet (HMMBF) (per liter)

* Children with AD show positive skin tests to foods and food specific IgE 
* Immediate food allergic reactions in children with AD: Cutaneous: Contact urticaria Generalized urticaria Non cutaneous: Vomiting Diarrhea Rhinitis etc.

Table 5: Data in Favor of the Relationship between Atopic Dermatitis and Food Allergy

Table 6: Contributory factors to the unreliability of diagnostic diets in atopic dermatitis

When a child shows a clear-cut improvement after the 4-week diet, a challenge test should be performed. This test, although time-consuming and sometimes even harmful, is necessary owing to the lack of any other reliable in vivo or in vitro test for the diagnosis of FA. It is generally agreed that the diagnosis of FA should be always confirmed by DBPCOCF. Usually the offending food is marked in gelatine capsules. However there exists no general agreement on the amount of food, fresh or lyophilized to be administered or on the procedure of administration to be followed. When children or infants are not able to swallow capsules, the taste of the offending food can be masked in other items [23].

The clinical accuracy of SPTs depends on the standardization of food-allergen extracts. Since variations in these extracts may influence the results, it is necessary that their preparations be purified and standardized to minimize the risk of unreliable results. However the positive predictive accuracy of skin test to foods is about 60%, hence the challenge test is imperative for the diagnosis of FA [13,23].

Since history is questionable especially regarding the prediction of immediate reactions, challenge tests in children with positive SPTs and/or RAST should always be done with precaution. The pretty good negative predictive accuracy of SPTs permits exclusion of immediate reactions following the challenge test. Methods for the detections of IgE antibodies to foods suffer from the same limitations of SPTs [12].

### Treatment

#### Elimination of the offending food

The elimination of the offending food (s) is mandatory in children with FA-induced AD. The most common offending foods are CM and egg. Hyper-sensitivity to CM is an important contributory factor in atopic dermatitis. CMA peaks in infancy, when CM is an important source of nutrients. We all know that 500 ml of CM provides a 2-year-old child with 100% calcium, 50% protein, 24% energy, and 100% riboflavin of the recommended intake for age. In addition, this high nutritional value is associated with a low cost. Therefore the correct choice of a CM substitute is a prerequisite for feeding babies with CMA. CMA is also a genetic disease, since parents In Tables 7 and 8 are summarized the main properties of SPS [28]. Contrary to HFs

| No minute amount of CM proteins. No cross reactivity with CM protein. Lower immunogenicity (IgE Abs) than CM proteins. Lower allergenicity than CM proteins. Similar antigenicity (IgG, Abs) to CM proteins. Nutritional adequacy similar to CM formulas. Better palatability than highly hydrolysate formulas. Less expensive than highly hydrolysate formulas. |

Table 7: Properties of Soy-proteins-based Formulas

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<thead>
<tr>
<th>HF</th>
<th>Casein</th>
<th>SPF Whey</th>
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<tbody>
<tr>
<td>Immunogenicity (IgE)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Antigenicity (IgG)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Allergenicity</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Cross-reactivity with IgE Abs to CM</td>
<td>+</td>
<td>++</td>
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Table 8: Immunogenicity and cross-reactivity of HFs and SPS
which may contain native proteins from which the product is derived, no minute amount of intact CM proteins are present in SPPs. Soy proteins are immunogenic, but according to experimental and clinical studies, they are less immunogenic and allergenic than CM proteins. SPPs do not cross-react with CM proteins, while HFs do [26,27]. As we first reported, whey and partially HFs can trigger anaphylactic reactions, which may be even life-threatening, in infants and children with IgE-mediated CMA [25-27]. Due to residual allergenic epitopes and contamination with minute amount of intact proteins, these products are not safe for children with IgE mediated CMA, while extensively HF are safer and useful in young babies with CM and/or soy enteropathy. Soy proteins are antigenic as CM proteins, but as previously alluded to this should not be regarded as harmful. SPPs are nutritionally sufficient, the taste is well accepted by most infants and, although SPPs are expensive, they are cheaper in comparison to HFs [28].

Therefore SPPs should be the preferred choice in children with IgE-mediated CMA and casein highly HFs should be tried when there is definitive evidence that the child is allergic to soy [29]. Whey partially HFs should never be used in infants with IgE-mediated CMA and due to the very good negative predictive value of SPTs to highly HFs should be performed before giving this products to babies with CMA [26,27].

Therapeutic advances include tacrolimus, a topical ointment for the treatment of AD, which dramatically improves the clinical appearance and degree of itching [30].

## Conclusion

Significant progress has been achieved in the understanding of FA. The institution of standard definitions for the clinical presentations of FA will render the scientific literature more discernible. It may be speculated that also in AD the allergens could induce a cutaneous hyper-reactivity analogous to the bronchial hyper-reactivity seen in patients with asthma [17]. This in turn could lower the pruritus threshold for a wide range of nonspecific stimuli such as irritants, heat, humidity, stress, and the like. Eosinophils, as in asthma, seem to play a crucial role in inducing and maintaining the skin lesions. These critical data suggest that in AD there exists a vicious circle, orchestrated by immunologic and non-immunologic factors acting in varying ways and at different levels triggering different, though synergetic, reactions to initiate, amplify and maintain the chronic skin lesions characteristic of the condition. It is likely that the next coming years will witness the development of new strategies for the prevention and treatment of AD, aimed at specific targets based on a thorough understanding of its pathogenesis.

## References