

Guideline

Approach to suspected food allergy in atopic dermatitis

Guideline of the Task Force on Food Allergy of the German Society of Allergology and Clinical Immunology (DGAKI) and the Medical Association of German Allergologists (ÄDA) and the German Society of Pediatric Allergology (GPA)

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Summary

The following guideline of the "Arbeitsgruppe Nahrungsmittelallergie der DGAKI" (Task Force on Food Allergy of the German Society of Allergology and Clinical Immunology) and the ÄDA ("Ärzteverband Deutscher Allergologen", Medical Association of German Allergologists) and the GPA (German Society of Pediatric Allergology) summarizes the approach to be taken when food allergy is suspected in patients with atopic dermatitis (neurodermatitis, atopic eczema). The problem is clinically relevant because many patients assume that allergic reactions against foods are responsible for triggering or worsening their eczema. It is important to identify those patients who will benefit from an elimination diet but also to avoid unnecessary diets. Elimination diets (especially in early childhood) are associated with the risk of malnutrition and additional emotional stress for the patients. The gold standard for the diagnosis of food-dependent reactions is to perform placebo-controlled, double-blind oral food challenges because specific IgE, prick tests and history often do not correlate with clinical reactivity. This is particularly true in the case of delayed eczematous skin reactions. Diagnostic elimination diets should be used before an oral

provocation test. If multiple sensitizations against foods are discovered in a patient, an oligoallergenic diet and a subsequent stepwise supplementation of the nutrition should be performed. If a specific food is suspected of triggering food allergy, oral provocation should be performed after a diagnostic elimination diet. As eczematous skin reactions may develop slowly (i. e. within one or two days), the skin be inspected the day after the provocation test and that a repetitive test be performed if the patient has not reacted to a given food on the first day of oral provocation. The guideline discusses various clinical situations for patients with atopic dermatitis to facilitate differentiated diagnostic procedures.

Introduction

Food has been discussed as a possible trigger of flares of atopic dermatitis for years. Many patients believe that allergic reactions to food cause or maintain their eczema. The majority of patients try diets during the course of the disease which can result in malnutrition and emotional stress [David 1984]. Most investigators consider food allergy to be a trigger factor for atopic dermatitis especially in childhood, because food allergies of the immediate type are of importance primarily in childhood and are often lost later in life. In one study, about 1/3 of all children with severe atopic dermatitis had a food allergy [Johnston 2004] (Table 1). Table 1 summarizes those studies in which children with atopic dermatitis were tested for food allergy using a blinded oral challenge. Unfortunately, in many studies where oral provocation tests were performed, deterioration of the dermatitis, which is usually first seen on the following day, was not systematically assessed. For adults, there are no studies with a sufficient number of patients exist to determine the frequency with which the affected also react to pollen-associated food in particular with exacerbation of dermatitis.

Clinical reaction patterns to food in atopic dermatitis

Provocation tests can lead to three different reaction patterns in patients with

atopic dermatitis [Werfel, Breuer 2004]:

- 1. Non-eczematous reactions are usually IgE-mediated and present on the skin as pruritus, urticaria or flush reactions, as well as with other immediate-type reactions of the gastrointestinal or respiratory tracts or as anaphylaxis.
- 2. Isolated eczematous delayed reactions, i. e. usually flare of eczema after hours or 1 to 2 days.
- 3. A combination of non-eczematous early reaction and eczematous delayed reaction.

While food as trigger of immediate-type reactions can be classified relatively well by a detailed history, skin tests and demonstration of specific IgE towards the suspected food, the identification of a trigger of delayed reactions such as eczematous reactions in atopic dermatitis is difficult. Here late reactions to food can occur in an isolated fashion or be coupled to a previous immediate-type reaction [Werfel, Breuer 2004]. Analyses of provocation tests in children show that about 25 % of all clinical reactions occur only after two hours or later [Celik-Bilgili 2005, Breuer 2004]. Patients with birch pollen sensitization can also react to oral challenge with cross-reacting foods with exacerbation of eczema [Breuer 2004]. Triggering of atopic dermatitis by pollen-associated food is especially relevant for adolescent and adult patients. In terms of an unselected population the inducibility of dermatitis by pollen-associated food appears to be low [Worm 2006]. Besides the frequently blamed “classical” food proteins, there are indications that other food ingredients can exacerbate atopic dermatitis in individual patients. Whether these reactions are allergic or non-immunologic, pseudoallergic reactions, is not clear yet [Worm 2000]. Sugar as trigger factor plays no role according to the results of provocation tests and is overestimated by many patients or their parents [Ehlers 2001].

Practical aspects of diagnostics

The “gold standard” in diagnostics of food-dependent reactions is placebo-controlled, double-blind challenge [Bindsløv-Jensen 2004], as specific IgE, prick tests and history often do not correlate with clinical findings [Atherton 1978, Niggemann 1999, Breuer 2004].

Table 1: Prevalence of food allergy in children with atopic dermatitis.

Authors	Year	N	Allergy (%)
Sampson	1985	113	56
Burks	1988	46	33
Sampson	1992	320	63
Eigenmann *	1998	63	37
Burks	1998	165	39
Niggemann	1999	107	51
Eigenmann*	2000	74	34
Breuer	2004	64	46

*Unselected children with atopic dermatitis
Food allergy confirmed by double-blind placebo-controlled oral challenge

Table 2: Diagnostic tools to clarify food allergy in atopic dermatitis.

History (minor role in the case of delayed flares of atopic dermatitis)
Symptom-food diary
In-vitro tests:
Specific IgE (together with total IgE)
In-vivo tests:
Skin tests
Oral provocations

In the diagnosis of food allergy in atopic dermatitis no single confirming parameter exists [Niggemann 2006]. A stepwise approach taking individual factors into consideration is also sensible here. Food allergy diagnostics in atopic dermatitis does not differ in principle from diagnostic in other allergic diseases (Table 2). The following section summarizes published recommendations for the approach to IgE-mediated reactions to food [Niggemann 2006] and stresses the peculiarities in atopic dermatitis. History is the first piece of the diagnostic puzzle when food allergy is suspected. With the help of the history an association between clinical symptoms and the ingestion of certain foods can be made and indications of IgE-mediated reactions can be attained. In one of the few placebo-controlled studies on elimination diets, improvement of eczema was observed in 60 % of the children by avoidance of egg and milk. Often the parents’ suspicion on the role of milk or egg

as trigger factor of eczematous skin lesions does not correlate to observations made in the children [Atherton 1978, Niggemann 1999, Breuer 2004], which actually does suggest the low value of history for eczematous reactions. In retrospective studies on the value of diagnostic instruments in patients with atopic dermatitis who had blinded oral challenge, history again did not have a high diagnostic specificity [Breuer 2004]. When food allergy is suspected *in vivo* tests (e. g. skin tests) and/or *in vitro* tests (e. g. specific serum IgE) should follow. As skin test for routine diagnostics, only the prick test is recommended. A further diagnostic instrument in the work-up of food allergies is patch testing with native foods (termed atopy patch test). Atopy patch test can be recommended as an additional diagnostic tool in specialized centers in the following situation:

- 1. Clarification of a food allergy in atopic dermatitis without identification of an IgE-mediated sensitization.

2. Severe or persistent atopic dermatitis with unknown trigger factors.
3. Multiple IgE-mediated sensitizations without proven clinical relevance in patients with atopic dermatitis [Turjanmaa 2006].

The atopy patch test is not generally recommended for routine diagnostics. Larger numbers of patients have been studied only in the younger age group where the atopy patch test was not able to significantly reduce the necessity of oral challenges [Mehl 2006]. A current position paper of the DGAKI exists on *in vitro* diagnostics of food allergy [Kleine-Tebbe 2001]; determining specific IgE concentrations is the routine standard. Probably the positive predictive value for clinical reactions in patients with atopic dermatitis based on the specific IgE concentration depends on the particular food [Sampson 2001, Celik-Bilgili 2005]. At present, a correlation between specific IgE titers is available only for cohorts of children and only few foods. In particular no corresponding studies on eczematous reactions to food in atopic dermatitis have been performed.

The lymphocyte transformation test (LTT), as a supplemental instrument in the *in vitro* diagnostics of cell-mediated allergy, plays a role only in the realm of scientific studies.

In case of unclear relationships, a *symptom-food diary* is recommended. Such diaries, e. g. over a time period of two to four weeks, give an overview of food ingested as well as the lifestyle of the patient and can perhaps, at times, even allow for the association of symptoms with certain foods.

If after this an association of disease manifestations with the ingestion of certain foods is not possible (especially with regard to the exacerbation of atopic dermatitis), the patient can be placed on an *oligoallergenic basic diet*. For infants the oligoallergenic basic diet should consist of an extensively hydrolyzed protein formula; for older patients the foods listed in Table 3 rarely cause allergy and can be employed. In adult patients this approach is needed only in exceptional cases. In case of corresponding sensitization, it is usually more sensible to first try a pollen-associated elimination diet in this age group.

The individual components of the oligoallergenic basic diet must of course be

Table 3: Example of an oligoallergenic basic diet.

Grain: white rice
Meat: lamb, turkey
Vegetables: cauliflower, broccoli, cucumber
Oil: refined vegetable oil, non-dairy margarine
Beverages: mineral water, black tea
Spices: Salt, sugar

determined on an individual basis and can be combined freely. This can be oriented on the specific IgE antibodies. In some instances one will have to retain foods against which a weak sensitization exists in the regimen. Even hydrolyzed protein preparations can cause symptoms up to anaphylactic reactions [Buscino 1989, Niggemann 1999, Rosenthal 1991].

When a diagnostic diet does not result in an improvement of clinical findings (i. e. eczema) after four weeks at the latest, the relevance of a food allergy for the patient's symptoms is improbable. In this case provocation tests are usually unnecessary as are dietary restrictions. When deterioration occurs after the introduction of another diet, the possibility must be considered that the patient actually reacts clinically to a component of the oligoallergenic diet or that other trigger factors were acting during the elimination phase (e. g. increased pollen levels, mental stress). In rare cases objective symptoms to foods in the basic diet must be considered. When an improvement of signs and symptoms is observed, *oral provocation tests* follow.

Patients with atopic dermatitis with recent clear immediate-type reactions to food usually do not undergo provocation testing [Bahna 1994]. Patients with atopic dermatitis and pollen-associated food allergies in the sense of an oral allergy syndrome (OAS) [Breuer 2004] usually can be diagnosed on the basis of clinical findings together with the corresponding sensitization pattern and do not necessarily require oral provocations.

Open oral provocation has significance for diagnostics especially in the case of negative results. Limitations of open provocation testing are set by psychological factors, lack of objectivity and the expected delayed reactions in atopic dermatitis [Niggemann 2006]. Therefore, for unclear reactions in the course of an

open oral provocation test, repetition in form of the more time-consuming but more secure to interpret blinded oral challenge is strongly recommended.

Before radical dietary measures (e. g. cow's milk-free diet for infants and small children) as well as in severe atopic dermatitis, oral challenges should primarily be performed on a double-blind and placebo-controlled basis. With this test method – independent of subjective factors – the clinical relevance of existing sensitizations or allegedly observed symptoms can be ascertained. Detailed instructions on performing the double-blind and placebo-controlled oral provocation (DBP-CFC) can be found in the position paper of the DGAKI by Niggemann et al. [2006]. With regards to atopic dermatitis it is stressed that

1. An oral provocation test is urgently recommended even if the skin improved during a diagnostic elimination diet. It is usually not sufficient to trust the result of a diagnostic elimination diet as a variety of influencing factors exists.
2. Patients with proven immediate-type reactions do not undergo oral provocation to prove the role of the food for eczema.

Recipes for blinding food allergens can be found in Werfel and Reese et al. [2006].

In atopic dermatitis oral provocation should occur in the symptom-poor interval after an elimination diet. If a stable situation cannot be attained by avoidance alone, topical therapy must be intensified before the provocation and continued in the same fashion. Accompanying therapy and conditions should be changed as little as possible. Only a continually stable situation is the basis for evaluating clinical reactions. If a corticosteroid is absolutely necessary, then the application of a weak preparation (e. g. 1 % hydrocortisone) once daily is possible. Clinically relevant reactions will not be

prevented by this – while on the other hand natural fluctuations of the eczema are balanced. Steroid therapy should be continued over the entire provocation; no antihistamine or UV therapy should be given. During provocation, food should be given on an empty stomach, which is not always possible in infancy. The dose should be increased every 30 (–60) minutes up to the highest dose or until a clinical reaction occurs.

The total dose should approximately correspond to the average daily intake (e. g. one egg, 150 mg milk). Due to the expected delayed reaction, the skin must at least be inspected on the day following the challenge. Optimally, the observation period should be at least 48 hours. In atopic dermatitis repetitive provocation with the same food for at least two days (Table 4) should be performed. The clinical evaluation must be uniform throughout the period (e. g. SCORAD: Assessing eczema severity [European Task Force on Atopic Dermatitis 1993]). Even when no immediate-type reactions are reported, provocation should only be performed by those with clinical experience in allergic diseases. Especially in children with atopic dermatitis who have been on an elimination diet for a longer period of time, very severe to life-threatening reactions upon re-introduction of a food have been reported [Flintermann 2006].

Emergency equipment and medications must be available.

As severe symptoms up to lethal reactions are possible after food challenge in highly sensitized patients (even with an unclear history for severe clinical reactions) [Canadian Paediatric Society 1994, Sampson 1992], oral provocation should be initiated in the form of a titration – especially when immediate reactions are feared. Immediate-type reactions often occur at low allergen doses even in patients with atopic dermatitis [Sampson 1985]. Special caution should be taken after long-term avoidance (e. g. a long time interval after the last administration of the food and re-challenge). Further technical points on provocation are discussed in detail in the guideline of Niggemann et al. [2006].

Oral provocation tests after elimination or oligoallergenic basic diet can take the form of a stepwise introduction of individual foods, when there are no indications of immediate-type reactions. This

Table 4: Course of repetitive provocation tests in atopic dermatitis.

Day 1*	Titration of verum up to daily dose corresponding to age
Day 2*	Verum (daily dose corresponding to age)
Day 3	Observation
Day 4*	Titration of placebo
Day 5*	Placebo (in same amount as verum on day 2)
Day 6	Observation

* Verum or placebo (days 1 + 2 and 4 + 5) are administered in random order in double-blind provocation

Table 5: Example for order for provocation or reintroduction of food after an oligoallergenic basic diet.

1. Cow's milk (perhaps soy)
2. Hen's egg
3. Wheat products
4. Further vegetables (e. g. potato, carrot)
5. Fruits (e. g. banana, sweet pear)
6. Further grain varieties
7. Further meat varieties
8. Others: nuts, celery, spices

can, for example, be done on the order presented in Table 5. Every four to seven days a new food is introduced and retained in the diet. Many challenges will only be possible on an open basis and not as placebo-controlled tests. If outpatient testing or history gives rise to ambiguities, performing DBPCFC is indicated.

Which approach for which constellation in atopic dermatitis?

On the basis of history and the results of clinical examination (severity of atopic dermatitis) the following constellations with regard to possible food allergies can be differentiated with each requiring a different approach:

- 1. Atopic dermatitis exists and there is a clear history of current immediate-type reaction to food. Independent of the severity of atopic dermatitis it is recommended after confirming specific sensitization (*in vitro* test/ skin test) to perform an elimination diet and perhaps oral provocation as recommended in the guidelines of Niggemann et al.
- 2. Atopic dermatitis exists as well as a clear history of an immediate-type

reaction that occurred a half year or longer ago. In small children the current status of the immediate-type reaction must be determined, as tolerance might have developed in the meantime. The approach again consists of identifying sensitizations, elimination diet and oral provocation.

- 3. Severe atopic dermatitis is present, but no clear history of an immediate-type reaction. The association between eating certain foods and eczematous skin lesions is unclear. We recommend checking for a specific sensitization to important basic foods in a screening test in serum or in a skin test. In the case of a mono-sensitization or a sensitization with a particularly high degree of sensitization a targeted elimination diet and oral provocation can follow. In polyvalent sensitizations an oligoallergenic diet with subsequent oral challenge of the most important foods as described above is recommended.
- 4. Atopic dermatitis is present and an association with eating certain foods is suspected by the patient or the parents, perhaps an elimination diet is

already being adhered to on the basis of this suspicion. Independent of the severity of atopic dermatitis, a specific sensitization should be searched for here and the clinical relevance of the food should be tested in a double-blind oral provocation. This is especially advisable when important basic foods are being avoided in infants and small children in order to end unnecessary diets.

The great expense of DBPCFC is especially justified and necessary for the often very young patients in order to avoid foods causing certain clinically manifest reactions, but also to protect our patients from uncertain to even senseless diets that unnecessarily harm the patients, cause considerable nutritional deficiencies, unfairly exempt therapists from responsibility and prevent sensible therapeutic measures.

Even dietary recommendations based on solid provocation tests are only valid for 12–24 months in childhood. After this, the current clinical status must be newly evaluated by renewed determination of specific IgE as well as an oral provocation test. For adults and for certain allergens (for example nuts, peanuts, fish), longer intervals might be applicable. Physician's dietary recommendations should only be in form of comprehensive dietary counseling with the aid of a dietician. Current dietary recommendations developed along with dieticians are available [Werfel and Reese et al. 2006].

Introduction of additional food in infants and small children with clinically manifest atopic dermatitis:

Regardless if atopic dermatitis appears during the first half year of life or not, the infant should be breastfed exclusively ideally for six months but at least for four months. As an alternative to breastfeeding for infants with an allergy risk (presence of atopic manifestations in at least one first-degree family member) it is recommended to use a hydrolyzed infants' formula. The GINI study suggests that especially in families with at least one member having atopic dermatitis, extensive hydrolysates based on casein have a greater preventive effect than other hydrolyzed infants' formulas [von Berg et al. 2003]. Further, this study dramatically shows that only hydrolysates that have proven their protective effect in studies can be recommended for preven-

tion. If a severe atopic dermatitis develops in infants who are still exclusively being breastfed, there are indications that it might be sensible to shorten the breastfeeding period in individual cases [Isolaure 1996]. Before such a step, it should be determined if the eczema resolves when the mother avoids certain allergens. A suspected food allergy must be confirmed by the re-introduction of incriminated food in the mother's diet, before the mother goes on a long-term elimination diet during breastfeeding. When an elimination diet is therapeutically justified, comprehensive nutritional counseling by dietician with allergologic expertise must be done in order to avoid nutritional deficiencies in mother and child.

If the mother wishes to discontinue breastfeeding completely in the 2nd half year of life, no special formula is required as substitute for breast milk. A normal infant starter pre- or No. 1 formula based on cow's milk can be given. The use of a soy based formula that might be considered in the presence of cow's milk allergy is not associated with an increased allergy risk in the 2nd half year of life [Klemola et al. 2002, Zeiger et al. 1999]. The slow and perhaps late (after the 6th month of life) introduction of additional food is still an important measure in allergy prevention in infancy, even if little evidence can be found for this approach. Current studies show that even starting additional food after the 4th month as recommended for children without a positive family history is not associated with an increased allergy risk [Zutavern et al. 2006]. Above all, the introduction of additional food should occur slowly, so that an intolerance of a newly introduced food can be recognized quickly. It is advisable to document reactions in a symptom diary with the start of additional food.

The introduction of additional food starts at lunch. Per week only one new food is added initially, so that it takes a month to develop a complete vegetable-potato-meat purée. Later, the intervals can be reduced to three to four days. All foods are first introduced in cooked form. The use of prepared small children's food in jars guarantees high controlled quality and is quite suitable, as long as the jar has a simple composition. Self-preparation is more time-consuming, but with careful and correct preparation

it offers the chance of determining the composition of the ingredients oneself.

Even if some infants do not tolerate carrots, usually carrot purée is the first food introduced. Its sweet taste makes it well-suited to accustom the infant to purée meals. Other vegetables (e. g. cauliflower, broccoli, kohlrabi, zucchini, fennel) are suitable as long as they are self-prepared or available as jars with a single food. Potato and lean meat (poultry, lamb, veal, beef) follow. Later, further tolerable vegetables can be introduced. The addition of high-grade salad oils (rape, sunflower, corn or soy oil) at lunch ensures the adequate supply of important fatty acids. As the use of refined and thus non-allergenic oils is recommended, no special testing of oils used is necessary.

In the second half year of life, the whole milk-grain porridge is introduced. If a proven cow's milk allergy exists at the time of introduction, the milk is replaced by a tolerated infant formula. Avoiding cow's milk in the second half year of life is not justified for purely preventive grounds due to the high nutritional value of milk. Introduction can also be delayed for a month by moving up the grain-fruit porridge. Rice flakes should be used as grain first to be replaced later with other grains such as oats and millet due to their higher iron content.

The grain-fruit porridge can initially be prepared with cooked fruit (apple, pear or banana) together with grains already introduced. If a variety of fruit is tolerated in cooked form, it can also be tested raw.

After introduction of the above foods, further foods may be introduced on an individual basis; an interval of three to four days should be observed if possible. Due to the high allergenic potential and the significantly poorer prognosis in case of manifest allergy, nuts and peanuts should be avoided in the first years of life. Egg and fish can be introduced at the time of the first birthday at the latest.

Conclusions

The problem of suspected food allergy in atopic dermatitis is clinically relevant, because many patients or their parents presume that allergic reactions to food can cause or worsen dermatitis and a subgroup of these patients actually profit from an elimination diet.

A stepwise diagnostic approach considering the various clinical constellations

which are discussed in this guideline allows for a differentiated approach to patients with atopic dermatitis and suspected food allergy.

Procedure in creating consensus

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