

Short communication

Diagnostic pitfalls in food allergy in children

Currently, the diagnostic work-up of suspected food allergy includes skin prick tests, the measurement of food specific immunoglobulin E (IgE), and the atopy patch test, and double-blind, placebo-controlled food challenges. However, all of these methods, even double-blind, placebo-controlled food challenges (DBPCFC), may sometimes be misleading. This overview describes several pitfalls for standard diagnostic methods such as problems with irritative skin reactions mimicking IgE-mediated symptoms, the problem of non-IgE-mediated reactions, pitfalls arising from the way foods are prepared or processed, effects of the route of exposure, the role of augmentation factors lowering the threshold value for clinical reactions, the noncomparability of specific IgE decision points, the influence of the timing of diagnostic measures. In addition, the problem of alternative diagnostic measures is discussed. In conclusion, there are several pitfalls in the diagnostic work-up of food allergy, which may be misleading for the physician. Properly performed controlled oral food challenges still represent the gold standard for implementing specific diets in food allergic individuals in order to avoid both unjustified diets, which may lead to severe impairments in growth and development, and to avoid unnecessary symptoms if an underlying food allergy is not correctly identified as a cause for the symptoms of the patient.

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Food allergy represents a major allergological problem in infants and children. Clinically relevant food allergy is reported in around 40% of children with atopic dermatitis (AD) (1–3). Among the most common offending foods in children are cow's milk (CM), hen's egg (HE), wheat, soy and peanut (3, 4).

The diagnostic work-up of suspected food allergy includes skin prick tests (SPT) (5), the measurement of food specific IgE antibodies using serologic assays (6, 7), and more recently the atopy patch test (APT) (8, 9), although double-blind, placebo-controlled food challenges (DBPCFC) still represent the 'gold standard' for diagnosing food allergy (3, 10–13). However, even DBPCFC may sometimes be misleading. Various other tests, such as the scratch test, intradermal test or the labial test do not seem meaningful in the diagnostic work-up of food allergy.

This overview describes several typical situations, which may be encountered during the diagnostic work-up of food allergy, and aims to highlight possible pitfalls in order to avoid nonjustified diets, which may lead to severe impairments in growth and development.

Nonallergic skin irritations

Among the most common immediate skin symptoms observed in oral food challenges – next to acute urticaria – is the occurrence of a flush or erythema. This can be

immunoglobulin E (IgE)-mediated but it may be the result of a nonspecific irritation of the skin due to acids contained in a variety of foods – especially in citrus fruits (14). This does not lead to life threatening reactions and strict avoidance is not mandatory. For the proof of IgE-mediated reactions, the IgE tests (specific IgE in serum or SPT) are mandatory.

'Irritations' of the skin (e.g. by citrus fruits) may mimic IgE-mediated reactions. Avoidance is only necessary for the patients' convenience in such cases.

Sensitization vs allergy

IgE-mediated sensitization can be determined by skin prick testing or by measuring specific IgE levels in serum. Both methods indicate that the immune system of the individual has responded to a foreign protein by producing IgE antibodies, e.g. to CM or HE. However, this is by no means identical with a clinical relevant IgE-mediated allergy, which requires typical immediate type clinical symptoms (e.g. urticaria) or late phase symptoms (exacerbation of underlying eczema) after consumption of the food in question.

The situation is especially difficult if the patient has very high total IgE levels, e.g. several thousand international units (15). Often, these patients show specific IgE to nearly every aero- and nutritional allergen investigated,

and *in vitro* allergy testing may not provide any important information in terms of a potentially necessary diet. This shows that the sensitivity of specific IgE determination in serum is high, but the specificity is poor. The final diagnosis of food allergy should in these cases rely solely on oral food challenges.

Not every patient who has positive IgE tests (and is therefore sensitized), has a clinical relevant allergy. Clinical actuality of a given sensitization should be proven by oral food challenges – especially in patients with very high total IgE concentrations. In some cases, IgE testing fails to add to the diagnostic work-up of food allergy.

Diagnostic decision points

In several publications, so-called diagnostic decision points have been proposed to identify the patients with a particular food allergen-specific IgE who are probably reacting to food. A 95% predicted probability values have been described with 15 kU/l for CM, 7 kU/l for HE and 14 kU/l for peanut (6). Other authors reported 5 kU/l for CM (16). A 100% predicted probability value of 57.0 kU/l has been described for peanut (17). However, own unpublished data revealed 95% predicted probability values of 46 kU/l for CM, and 10 kU/l for HE. There are various possible explanations for these differences, such as that the median ages in the study populations and the percentage with AD as an underlying disease are not comparable or that in most other studies late phase clinical reactions were not considered, while in our studies 50% of children showed late or combined (early plus late) clinical reactions during oral challenges. However, these parameters do not seem to explain all the observed differences. Additional prospective multicentre studies with large patient populations will be necessary to solve this problem. Special care should be taken to separate children with first manifestation of their allergy from patients being re-evaluated for their allergy.

Currently, diagnostic decision points for food specific IgE values are only valid for the specific population studied. In addition, decision points are not established for many foods (e.g. tree nuts, shell fish), and in several cases the positive predictive value (PPV) is less than 75% (e.g. wheat and soy). Therefore, no general recommendations can be made at the present time.

Time point of diagnostic work-up

Usually, food allergy is diagnosed during the first months of suspected symptoms, and the determination of specific IgE levels may be helpful in this situation (Fig. 1). In selected cases oral food challenges may become superfluous due to the high predictability of specific IgE decision points. However, the situation may be a different if the same *in vitro* tests are carried out during re-evaluation of

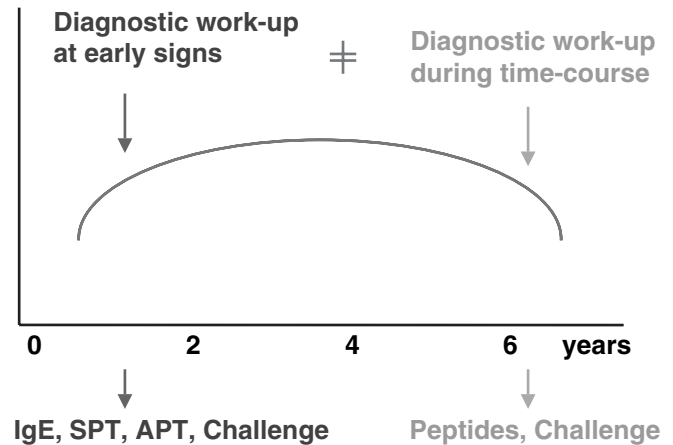


Figure 1. Implications of time point of the diagnostic work-up.

the patient. There are still conflicting views on whether changes in specific serum IgE levels predict the development of clinical tolerance (18, 19) and additional collaborative studies on large patient populations may be necessary to elucidate this aspect.

The validity of diagnostic measures is dependent on the time point of the diagnostic work-up. Currently, oral food challenges still represent the only tool to document clinical tolerance.

Non-IgE-mediated reactions

IgE-mediated sensitization can be shown in the large majority of cases with proven food allergy. However, in some 10% of children with AD and positive double-blind, placebo-controlled food challenges (DBPCFC) both the SPT and the detection of specific serum IgE are negative (20). Moreover, these children do not differ in terms of the outcome of the APT, the occurrence of early or late phase clinical reactions during oral food challenges, or in age. The only differentiating finding was that there was a higher proportion of positive wheat challenges in the non-IgE group, whereas in the IgE-positive group positive reactions to CM or HE were more frequent. In addition, a number of gastrointestinal disorders, including allergic eosinophilic gastroenteritis and food-protein induced enterocolitis, have been associated with food hypersensitivity. In the majority of these children no food-specific serum IgE can be detected using standard methods. The immunological reactions appear to involve Th2 cells that are activated by specific food proteins (21).

Around 10% of positive DBPCFC are not IgE-mediated. Therefore, not the proof of specific IgE, but the suspicion of food related symptoms should be the indication to perform oral food challenges – especially in the case of wheat. Otherwise some children will remain undiagnosed for food allergy, and be denied the benefits of a specific diet.

Route of exposure

Usually, a prerequisite for food allergy is consumption of the corresponding food. However, in rare cases of extremely sensitized individuals, inhalation of allergen molecules (e.g. in roast vapour) is sufficient to cause clinically relevant symptoms, including anaphylaxis (22–24). This has to be taken into account when patients report symptoms, which suggest food allergy but they credibly assure that they have not eaten the food.

Another unusual route of exposure to a food is contact urticaria. Some children show symptoms of acute urticaria during atopy patch testing or when a drop of milk is running down the skin, but tolerate the swallowed milk without overt clinical symptoms.

A nonoral route may lead to relevant clinical symptoms of food allergy. A thorough medical history is essential for a correct diagnosis. Furthermore, contact urticaria to food is not identical with food allergy. Before recommending an elimination diet, a titrated oral food challenge should be performed.

Preparation of foods

Foods are consumed in various forms, e.g. raw, boiled, baked or roasted. In some cases, such as for heat labile proteins, it is well known that the cooked food is better tolerated than the raw form. This has been shown for HE (25). Another typical example is the tolerance of cooked carrots in patients with pollen associated food allergy, while raw carrots lead to clear and reproducible clinical reactions of an oral allergy syndrome.

For the case of allergy to peanuts, it could be shown by SDS-PAGE and immunoblotting that the methods of frying or boiling peanuts, as practiced in China, appear to reduce the allergenicity of peanuts compared with the method of dry roasting practiced widely in the USA (26).

The way foods are prepared or processed influences the degree of their allergenicity. For oral food challenges, foods should be administered in the way the patient consumes it (e.g. roasted peanuts) or in the highest allergenic form (e.g. raw HE).

False negative tests

In rare cases, after a negative oral challenge in a clinic setting, patients report clinical symptoms after having consumed the food at home. It could be demonstrated in an Italian study that five of 193 (3%) children tolerated foods on challenges but developed immediate symptoms when the same preparation of foods was ingested openly at home the next day (27). The food allergy was afterwards confirmed by DBPCFC.

Higher or repeated doses of foods may lead to clinical symptoms not observed during single point oral challenges.

Therefore, negative oral challenges should be followed by repeated open challenges.

Augmentation factors

Sometimes foods induce clinical symptoms, while they are tolerated on other occasions. There are several possible explanations for this, of which augmentation factors are the most plausible. The best-known augmentation factor is physical exercise in the form of exercise-induced anaphylaxis (EIA). EIA means that both the food alone and the physical activity alone is well tolerated, while the consumption of the food followed 30–45 min later by physical exercise may lead to clear immediate type allergic symptoms – including anaphylaxis (28–31). Other augmentation factors are drugs (e.g. aspirin) (32, 33), alcohol, a warm bath or sauna, hormonal factors (e.g. menstruation), systemic mastocytosis as an underlying disease, or psychogenic factors (e.g. stress).

In some cases, foods may only lead to symptoms of allergy if augmentation factors (such as physical exercise) lower the threshold level for clinical allergic reactions. In the case of a suggestive history, but a negative oral challenges, the possibility of augmentation factors should be considered.

Alternative approaches to diagnosis

Although a considerable body of literature on therapeutic aspects of complementary and alternative medicine has been published in recent years, little is known about complementary and alternative diagnostic procedures. Several unconventional methods have been said to be useful for the diagnostic work-up of food allergy or even superior to conventional methods, and many patients seem to trust these methods more than conventional ones, leading to unjustified strict and dangerous diets. A review of the literature reveals that neither the determination of hair-analysis, cytotoxic test, kinesiology, iridology, or electrodermal testing (and even specific IgG- or IgG4 antibodies in serum), represent useful tests for the daily practice identifying individuals who require a specific diet and those who do not (34).

No unconventional approach can currently be recommended as an alternative or complementary component in the diagnostic work-up of food allergy.

Conclusions

There are several potential pitfalls in the diagnostic work-up of food allergy. Properly performed controlled oral food challenges still represent the gold standard for implementing specific diets in food allergic individuals in order to avoid both unjustified diets, which may lead to

severe impairments in growth and development, and to avoid unnecessary consequences if an underlying food

allergy is not correctly identified as a cause of the patient's symptoms.

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