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Monitoring of IgE-mediated food allergy in childhood

T Foucard¹ and G Lilja²

Department of Paediatrics¹, University Hospital, Uppsala; Department of Paediatrics², Sachs’ Children’s Hospital, Södersjukhuset, Stockholm, Sweden



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Testing for IgE-mediated allergy is performed to reach or refute a suspected allergy. But a positive test does only indicate sensitization and not necessarily clinical allergy. A diagnostic challenge procedure is therefore necessary. Also, in the phase of tolerance development a challenge is needed as clinical tolerance is reached before allergen-specific IgE antibodies have disappeared. During recent years, an increasing interest has been given to the possibility of using the concentration of specific IgE and the size of the skin prick test wheal to tell the optimal time to do a challenge without exposing the child to a risk of a severe reaction.

Conclusion: Algorithms on when to do and when not to do a food challenge may be useful but should be used with great caution. Reasonable consideration should be paid to the severity of previous reactions and the kind of allergen involved.

Key words: Algorithm, challenge, children, food allergy, IgE tests

T Foucard, Department of Paediatrics, University Hospital, SE-751 85 Uppsala, Sweden (Tel. +46 18 6119471, fax. +46 18 6615853, e-mail. tony.foucard@kbh.uu.se)



There is an increasing interest in allergy testing among children as a consequence of the increased prevalence of allergic diseases occurring in children during recent decades (1). Thus, the paediatric section of the

European Academy of Allergology and Clinical Immunology (EAACI) has recently published a position paper aimed at stimulating allergy testing within paediatric allergology (2). The diagnosis of food allergy

is of special interest as such allergies are common and some of them may be severe to life-threatening (3, 4). Furthermore, in contrast to allergies to inhaled allergens such as those from pollens, pet animals or house dust mites, allergies to foods are often transient, at least in young children (5). Allergy testing with food allergens is therefore not only diagnostic but also a tool to facilitate the decision as to when a challenge should be performed in a food allergic child to see whether tolerance has developed or not.

Diagnosis of food hypersensitivity

According to recommendations in a position paper from EAACI, hypersensitivity to food can be subdivided into allergic (immune mechanism) and non-allergic (non-immune mechanism) reactions (6). In turn, adverse reactions based on an immune mechanism include immunoglobulin E (IgE)-mediated, non-IgE-mediated, and probably mixed IgE- and non-IgE-mediated mechanisms.

The diagnostic approach to food hypersensitivity is mainly directed to detect IgE-mediated allergy and is based on a combination of history, clinical examination and demonstration of food-specific IgE to the suspected food, either with skin prick test (SPT) and/or measurements of IgE antibodies in serum. However, the presence of a positive skin prick test or IgE test only indicates sensitization and not necessarily a clinical allergy. But the larger the wheal size and the more IgE antibodies found, the greater is the probability of a clinical allergy. A challenge test with increasing doses of the allergen is the normal way to prove or exclude the presence of a clinical allergy.

In scientific studies, a double-blind placebo-controlled food challenge (DBPCFC) is the gold standard to diagnose a food allergy (7). But such challenges are time-consuming and thus expensive, and should therefore not be used in daily paediatric practice but in a few selected cases. Even if performed as single open challenge tests, they are not without risk or inconvenience to the patient, and therefore it would be nice if suitable cut-off levels for skin prick test wheal diameters and food-specific IgE tests could be found above which challenge tests should be avoided. To reach this goal, it must be shown in large patient groups that test levels above the cut-off value are associated with positive challenge tests in almost every patient, and that challenge tests become negative in almost all children with test levels below the cut-off value. During recent years, several publications have shown the usefulness of skin tests and IgE tests in this way, and suggestions have been made to use these results in clinical practice in order to facilitate the diagnostic work out (8, 9).

Algorithm for the diagnosis of food hypersensitivity

In this issue of *Acta Paediatrica*, Thong and Hourihane present an algorithm in which they suggest how to use the mean skin prick test wheal diameter and quantitative measurement of IgE antibodies to a food to handle food allergy in order to avoid unnecessary and risky food challenges (10). The algorithm is probably quite useful as a rough guide for those who are inexperienced in the field, but it should be used with sound judgement. Very few infants and young children are probably included in the results behind the algorithm, and it should therefore be used with great precaution on children during their first 2 y of life.

In the algorithm, four basic foods (milk, egg, wheat and soy) are discussed at the same time as a not-needed food (peanut). This involves a possible risk, as peanut allergy is especially dangerous. Peanut allergy, in addition to nut allergy, is the most common cause of severe and fatal food allergy reactions in north-west Europe and the US (11), and the intake is almost always accidental as the allergens appear hidden in other foods. Although sensitization may occur already during infancy, most children notice their peanut allergy during preschool and school years. The prognosis is not as good as for milk and egg allergy, but a few moderately sensitized children may become test negative and clinically tolerant within a few years (5, 12). This is, however, unlikely to happen in children with a severe peanut allergy with high concentrations of specific IgE. Therefore, the indication for repeated tests for peanut allergy to look for tolerance development is not as strong as that for basic foods such as milk and egg. Furthermore, as the risk of developing a severe reaction is especially high at challenge with peanut, a challenge should be performed with great restrictivity and only by a specialist with access to intensive care.

In contrast, basic foods should be introduced as soon tolerance develops. The kinetics of sensitization differ for different foods. Allergies to milk and egg are often transient in young children, but allergy to soy and wheat to a lesser extent. Sensitization to milk and egg usually starts during the first year of life in infants with a genetic predisposition for producing an IgE response to allergens in these foods. Normally, the response reaches its height during the 2nd or 3rd half-year period, and thereafter a decrease is seen in most children (13). In the most severely allergic children, it takes a longer time before the concentration peaks. During the very early phase of this sensitization period, severe allergic reactions can be seen in infants with low or only moderate concentrations of milk- or egg-specific IgE. When tolerance starts to develop, clinical tolerance is seen before skin tests or IgE tests become negative.

The basic message of the algorithm is thus sound, that a challenge can be performed when the prick test wheal

or the IgE test has decreased to a value of about $\frac{1}{4}$ of the cut-off level for a positive challenge reaction. But it presupposes that the results on which the algorithm is based are representative for children all over the world, which is not necessarily true. In a study of Danish children with egg allergy, no significant relationship was found between the specific IgE concentration and the challenge threshold level, and for a given challenge threshold dose the concentration of specific IgE varied up to a factor of 40 (14). The median age of the children in this study was 2.3 (0.5–4.9) y, indicating that the age of the group under study is important. Furthermore, in two other studies of young children with a median age of 16 and 13 mo, respectively, the cut-off level of egg-specific IgE in serum that would predict a clinical reactivity to egg white with a greater than 95% certainty was 0.35 kU/L in one study and 17.5 kU/L in the other (15, 16). In the Danish study, the corresponding figure was 1.5 kU/L (14). These differences probably reflect variation of the selection of patients.

Not only is the age of the patient important but also the dominating symptom and the main chock organ. A child with asthma and food allergy runs a greater risk of developing a severe reaction than a child with eczema and food allergy. Another point to make is that tolerance develops gradually, which is clinically important, at least regarding basic foods. Long before the child tolerates normal amounts of cow's milk, the parents may notice that an accidental intake of a small amount of milk in cooked food no longer gives any symptoms. It is a great relief to parents when their child tolerates small amounts of milk or egg in bread or cooked food, although larger doses still cause symptoms. There is no indication that tolerance development is delayed if the intake of these foods is increased along with tolerance development. It may happen, though, that a few children, who regularly consume small or moderate amounts of allergenic food, may seem to become more sensitive with time, but this is, in most cases, likely to be due to an increased reactivity caused by an ongoing allergic inflammation. These children improve when the allergenic food is temporarily withdrawn.

On the other hand, one should not push the re-introduction of an allergenic food too hard, because in the individual situation many factors may work together and the reaction threshold could be exceeded. In addition to the amount of allergenic food ingested, one such factor may be the previous handling of the food (storage, cooking, roasting, etc). Also, other foods consumed at the same time may contribute to symptoms by IgE- or non-IgE-mediated immune mechanisms or non-immune mechanisms. Some foods may non-specifically facilitate the absorption of allergenic food, e.g. an intake of alcohol together with shellfish, or, as recently described, the fat content of the food may influence the severity of a reaction (17). Exercise, intake of cold beverage or a present cold may also facilitate an allergic reaction (18, 19). All these variable factors may

explain why the severity of a food allergic reaction can show such variations in everyday life.

Concluding remarks

Access to simple algorithms about when and how to perform tests and food challenges in childhood in a journal of general paediatrics may involve a risk that non-experienced doctors will consider performing such tests. It should be emphasized that the evaluation of infants and young children with significant food allergy should always be made by an experienced paediatrician. Furthermore, every child who has had a previous severe food allergic reaction should be evaluated by a doctor with experience of anaphylactic reactions and with facilities to treat them.

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