

FOOD ANAPHYLAXIS

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SUMMARY: The author reviews some aspects of the worldwide problem of anaphylaxis to foods, regarding its prevalence, clinical manifestations and present classification as well as the preventive and therapeutic measures that are presently available. Some of the future therapeutic perspectives are also discussed.

Key-words: Anaphylaxis - Food - Review.

INTRODUCTION

The word anaphylaxis was coined in the beginning of the 20th century by two French researchers (Portier and Richet) to designate the unintended hypersensitivity reactions, sometimes fatal, observed after a second administration of a given substance to obtain a prophylactic effect. Therefore, the term anaphylaxis, that literally means "without protection", represents the opposite of prophylaxis.

Presently, anaphylaxis has been defined by the WAO nomenclature review committee as a severe systemic hypersensitivity reaction that endangers life. Anaphylactic reactions can be further divided in allergic and non-allergic. Allergic anaphylaxis could also be divided in IgE mediated and non-IgE mediated (1).

Non-allergic anaphylaxis is caused by non-immunological mechanisms, such as a high content of biogenic amines in several foods (strawberries, spinaches, fermented cabbages, etc) or by a direct degranulating action on mast cells (opioid drugs).

Food anaphylaxis is similarly defined with the additional information that the "offending" agent, i.e. the substance that caused the severe hypersensitivity reaction, is a food. In many cases, the ingestion of very small quantities of the food can induce such reactions (2). In extreme cases, contact with food

allergens through other routes such as inhalation (odours, cooking vapours, fine particle aerosolization) or percutaneous route can be sufficient to induce anaphylactic reactions (3).

Interestingly, food anaphylaxis can have also unexpected psychiatric or medico-legal implications. In peanut-allergic patients there is at least one report of a deliberate ingestion of peanuts as a suicide attempt (4) and peanuts could also be used as an easily available murder weapon in peanut-allergic patients, as recently suggested in the fiction book "The Da Vinci Code" (44). Furthermore, the distribution of peanuts aboard commercial flights in the United States has been prohibited due to severe reactions caused by unintended inhalation of aerosolised peanut allergens.

EPIDEMIOLOGICAL DATA

The first report in the literature of fatal reactions due to food anaphylaxis dates back to 1905, with the description of the death of a baby after a provocation procedure with cow's milk (5). In 1926 there is another death induced by a provocation test with peas (6) and since then, several reports appeared in the literature describing death induced by the ingestion of several different foods (peanuts, soy, fish, shellfish, cow's milk and many others). In the 90's, the first reports of deaths following inhalation of food allergens appeared in the medical literature (7-9). Nowadays, although peanuts, tree nuts, milk, seeds, fish and shellfish account for the vast majority of severe food anaphylactic reactions (10) practically almost any

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food has already been demonstrated to have the potential to cause anaphylactic reactions (11) isolated or in association with other factors (e.g. exercise) (12). Food anaphylaxis is the most common cause of anaphylaxis observed in the emergency department (10) and this aetiology should always be sought for in the differential diagnosis of idiopathic anaphylaxis. The incidence of food anaphylaxis is difficult to ascertain with a good degree of confidence. U.S. estimates point to a incidence of approximately 29.000 emergency visits each year, with an average of 120-150 deaths annually (10).

CLINICAL MANIFESTATIONS AND CLASSIFICATION

As in any other form of anaphylaxis, there is a predominance of mucocutaneous symptoms with urticaria/angioedema and erythema (predominantly of the face and neck). Gastrointestinal complaints such as vomiting, diarrhea or abdominal pain are more frequent in food anaphylaxis but most of the fatal cases dye of acute respiratory obstruction, especially if patients have concomitant asthma (13-15).

Anaphylaxis severity can be graded in 5 stages, grade 5 corresponding to death. Grades 1 or 2 have mucocutaneous manifestations accompanied by systemic symptoms that are usually non life-threatening. Grade 3 includes respiratory obstruction of variable degree and grade 4 includes cardiovascular collapse. Usually clinical symptoms begin about 30 minutes after ingestion, a mean delay superior to drug or venom anaphylaxis (13). However these timings can be quite variable and food anaphylaxis may appear immediately or very shortly after eating the "offending" food. As in other forms of anaphylaxis, biphasic reactions have been reported, justifying the need for a period of observation of no less than 24 hours. Isolated delayed reactions, without any immediate reactions, are extremely rare although already reported and confirmed with a provocation procedure (16).

RISK FACTORS FOR SEVERE FOOD ANAPHYLAXIS

Some clinical characteristics that are also risk factors for all forms of anaphylaxis have special relevance in food anaphylaxis (13,17-19)

■ **Age:** most severe food anaphylaxis occurs in adolescents or young adults that tend to overlook the strict food avoidance measures that are recommended;

■ **Asthma:** there is a bi-directional link between asthma and food allergy. On one hand, patients with asthma that also have food allergy tend to have more severe forms of asthma than similar patients without food allergy. On the other hand patients with food anaphylaxis that have concomitant asthma tend to have much more severe anaphylactic reactions;

■ **Multiple food sensitivities:** the tendency to cross-reactivity between different foods can pose important difficulties in complying with food avoidance strategies. It has also been suggested that patients who have IgE binding to multiple epitopes on the same food allergen may be predisposed to more severe reactions (20);

■ **Latex allergy:** food allergy is common in latex allergic patients and an anaphylactic reaction may be the first and presenting manifestation of food allergy in these patients;

■ **Specific food allergies:** there are important geographical differences, probably related to different dietary habits. For instance, in the U.S., U.K. and France tree nuts and peanuts are the main causes of fatal food anaphylaxis (18), while in Italy fish and shellfish are much more relevant. There are also several reports of anaphylaxis induced by grapes in Greek patients (21) and anaphylaxis induced by sesame seeds is particularly frequent in Israel and Australia;

■ **Prior anaphylactic episodes:** although seeming paradoxical, several deaths have occurred in patients who knew that their food allergy was the cause of prior anaphylactic reactions (22,23).

There are numerous papers dealing with cross-reactivity between different aeroallergens and food allergens. Most frequently these papers describe cross-reactivity between pollens and fruits or vegetables (for instance, graminaceae-rosaceae; birch-apple; mugwort-celery) (24), between allergens containing tropomyosin (mites-shrimp) or between latex and several vegetable foods, namely banana, avocado, chestnut and many others (25). There are also descriptions of less frequent cross-reactivities such as the bird-egg (26) or the cat-pork syndromes (27).

Although not always true, in patients with respiratory allergic disease due to pollens, the cross-reactive food allergy tends to be less severe than patients who are sensitised to those fruits but without pollen sensitisation. The latter are usually sensitised to lipid transfer proteins (LTP), which are very potent allergens that frequently induce anaphylactic reactions (28).

Cross-reactivity may also be seen between different foods (29), usually belonging to the same taxonomic family (e.g. rosaceae fruits, leguminosae, crustaceae) but cross-reactivity between foods belonging to different families does exist (e.g. peanut and tree nuts), with or without concomitant sensitisation to aeroallergens.

REACTIVITY THRESHOLDS

In IgE-mediated food allergies, the threshold dose inducing symptoms can be very small and can vary a great deal between different individuals, a fact that poses several problems to patients and to the food industry (30). Recently the European Academy of Allergology and Clinical Immunology has issued a position paper regarding the standardization of food challenges in patients with immediate reactions to foods, suggesting very low starting doses for several allergens (e.g. 0.1 mg for peanut and hazelnut; 0.1 ml for milk; 1 mg for egg and soy; 5 mg for shrimp or cod) and stressing that even these low doses may need further adjustments in individual patients (31).

Due to the very small doses required to elicit severe reactions, hidden allergens or contaminating allergens represent a major hazard to food allergic patients, being estimated that they are responsible for approximately 10-20% of food anaphylactic reactions. This fact underlines the absolute need for a correct and comprehensive labelling of all food products and for individualized producing lines to avoid allergen contamination in food processing procedures.

Regarding food contamination, recently attention has been drawn to the possibility of infestation of flour products with mite allergens, which has been shown in a recent study to happen in up to 7% of wheat flour packages in different supermarkets and homes (32). These mite allergens could therefore be inadvertently ingested and due to the extensive cross-reactivity between mite species and to the enzymatic properties of many of these allergens, that could facilitate intestinal penetration, some authors suggest that this contamination may go unsuspected and induce severe anaphylactic reactions (33,34).

DIAGNOSIS

As in other food allergies a detailed clinical history is essential, trying to evaluate the effectiveness of avoidance measures that patients have already undertook and the results of re-introduction procedures already performed by many patients. In food anaphylaxis this

is particularly important since, at least in severe reactions, provocation procedures can be life-threatening and therefore are contraindicated.

Besides a detailed clinical history, skin prick tests with commercial extracts or with fresh foods are the most useful diagnostic tests (19). However, serum specific IgE or specific IgE-binding bands identified by immunoblotting methods are also of value in the diagnostic work-up of food anaphylaxis. Other tests such as CAST or basophil activation tests may be useful in selected cases (35).

TREATMENT

Acute treatment of any anaphylactic reaction, irrespective of its aetiology, is based in the prompt administration of epinephrine, preferably by intramuscular route on the external face of the thigh since in this manner therapeutic plasma levels of epinephrine can be attained much sooner. Besides epinephrine, generous intravenous fluid replacement and oxygen supplementation should be immediately started, while placing the patient in Trendelenburg position. Other inotropic drugs or bronchodilator drugs may be necessary in some patients. Antihistamines and systemic steroids, although frequently used, are of unproven value in the immediate treatment of anaphylaxis. However they have usefulness in symptomatic treatment of cutaneous manifestations as well as in the prevention and treatment of delayed reactions.

After the acute episode it is mandatory to prescribe a self-injectable kit of epinephrine but it is not enough to prescribe it since several studies have demonstrated that only 50-70% of these patients have their kit available if necessary and only 30-40% of these know how and when to use it. Underlining the need for an intensive and recurrent patients' education is the finding that in children with prior anaphylactic episodes, less than 30% were treated with auto-injectable epinephrine in a second anaphylactic reaction (36).

Eviction of "offending" foods remains the mainstay of prevention, although the obvious and ever increasing difficulties of a comprehensive labelling that allows to correctly identify the presence of these allergens in the myriad of food-processed products that constitute at least part of the daily diet of most people (37).

Future prospects rely on several strategies with theoretical value but that have yet to prove their practical effectiveness (38). Some examples of these strategies are:

➤ Development of hypoallergenic foods by modifying their physico-chemical characteristics before or after harvest or by engineering recombinant proteins that lack the allergenic sequences of the original foods (39);

➤ Anti-IgE treatment does not cure food allergy but it may reduce the intensity of food allergic reactions and therefore reduce the likelihood of a severe anaphylactic reaction (40). This chronic treatment, although very expensive, could be indicated in patients who had already one or two life-threatening anaphylactic episodes and in whom there can be no reassurance of effective avoidance measures;

➤ Specific immunotherapy (SIT) to aeroallergens has been shown to improve manifestations of food allergy, at least in pollen and latex allergic patients (41). It is debatable if SIT to cross-reactive aeroallergens is indicated in severe food anaphylaxis.

➤ Desensitization with modified or recombinant food allergens has also been attempted in animal models of food allergy. DNA-based immunotherapy, whether using bacterial plasmid DNA encoding specific food allergens or immunostimulatory oligodeoxynucleotide containing CpG motifs conjugated with food allergens have been used with some success (38). Mutated allergenic protein immunotherapy or associating allergenic peptides with heat-killed *Listeria monocytogenes*, which is a strong inducer of IFN- γ production (42) have also demonstrated efficacy in animal models but it will be long before considering the possibility of its use in humans.

➤ Chinese herbal formulas have been shown to block anaphylactic reactions in murine models of peanut allergy and this protection can last as long as 5 weeks post therapy. This protective response was associated with downregulation of Th2 responses, suggesting that it may be a potentially safe and effective therapeutic option for food anaphylaxis (43).

CONCLUSION

Food anaphylaxis is not a rare event and it is one of the leading causes of anaphylactic deaths, especially in young asthmatic patients. Effective preventive avoidance measures are difficult to implement for several reasons. Therefore, patients' education is essential, not only for a correct assessment of allergenic content of processed foods but also to ensure the promptness of epinephrine treatment if anaphylaxis should occur. Future strategies may become effective tools and provide, besides their medical usefulness, some psychological benefits to patients suffering from this life-threatening condition.

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