Anaphylaxis (M Sánchez Borges, Section Editor)

Food-Induced Anaphylaxis Year in Review

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Opinion statement

Food allergy is increasing; as a consequence, food-induced anaphylaxis is also becoming a growing problem. Our understanding of the mechanisms of tolerance is still basic and requires much more research before it becomes helpful in guiding our interventions. However, empirical approaches with oral immunotherapy and food introduction manipulation appear promising, although standardization is required before employing them on a large scale. Furthermore, education and public health measures can be helpful for the increasing proportion of the population at risk.

Introduction

Food-induced anaphylaxis (FIA) can be a life-threatening emergency that requires immediate treatment and prompt actions. However, clinicians need to identify progression, as death can occur within minutes of ingestion of a reactive allergen [1] and rapid decision-making may alter significantly the outcome. In daily practice, diagnosis of anaphylaxis can be an arduous process [2, 3] especially at the first presentation, when symptoms are not typical and/or when the trigger food allergen is not obvious. Up to 20 % of cases of anaphylaxis present without a rash, and in such cases, wheeze or hypotension can be confused with other acute medical conditions. This leads to inaccurate diagnosis and record of incidence, which is also represented by the difficulty in coding anaphylaxis as a diagnosis and anaphylaxis as the underlying cause of death under the International Classification of Diseases (ICD) system [4, 5]. Where the diagnosis of an allergic reaction is established, the severity of the reaction can be underdiagnosed [6].

With numbers of food allergic patients increasing worldwide [7–10], it appears that the incidence of anaphylaxis is rising too, supporting the need for emphasis on the condition.

Taking the above into account, there are several unmet needs around food-induced anaphylaxis and its study is gaining momentum. A literature review and novel findings, reported in 2014, are presented in this article. Among the large volume of the literature, we aimed to identify the more novel and groundbreaking findings.

A PubMed search with the use of keywords '((food allergy AND anaphylaxis) OR (food anaphylaxis))' with a publication date within 2014 revealed 546 publications. Abstracts were screened for content, relevance and duplicates, limiting the number of studies to 119. After excluding reviews or case reports and focusing on publications with interesting and important new findings, 85 articles were retrieved in full text. Guidelines, several of which have been published in 2014, were included [3, 11•, 12–14]; four intriguing articles published in early 2015 were added.

Epidemiology of food-induced anaphylaxis

The lifetime prevalence and incidence estimates for FIA are difficult to ascertain due to underrecognition when presenting to emergency departments [6]. Furthermore, many episodes occur in the community and are self-limiting; therefore, no medical intervention or follow-up may have been sought. In the wider context, the prevalence and real incidence of food allergy remain uncertain [8–10, 15]. Assessment of food allergy prevalence is hampered by differences in study designs, age groups, geographic regions, and dietary habits [15–18].

According to Umasunthar et al. [19••], the incidence rate of medically coded FIA in food-allergic individuals was 0.14 per 100 person years, being higher (0.20 per 100 person years) in the 0–19-year age group. The highest rate (up to 7 per 100 person years) was observed in children between 0 and 4 years. Results from different studies have considerable variation; however, the general conclusion is that the rate is low.

In an attempt to record food allergy in patients with primary immunodeficiency diseases within the US Immunodeficiency Network (USIDNET), 40 of 2263 patients (1.8 %) reported food-related reactions, 20 % of whom had anaphylaxis [20].

Prevalence of anaphylaxis is equally difficult to ascertain. Regional, national databases, primary care and hospital databases [21•, 22••] have served as sources for extraction of anaphylaxis data. A lack of worldwide accepted clinical definition or criteria of anaphylaxis and inaccuracy in coding within the ICD coding system [23] contributes towards underdiagnosis and underreporting of FIA. The overall prevalence of anaphylaxis appears to be increasing [21•, 22••, 24••, 25].

Analysis from national anaphylaxis data from the UK [22••] during the two previous decades (1992–2012) revealed that hospital admissions due to anaphylaxis have increased to seven cases per 100,000 population per annum, yet the rate of fatal cases remained unaltered [22••, 26•]. The cause of anaphylaxis varies among different age groups with food allergy being the main cause during the first two decades of life [22••, 27•, 28••]. The fatality data from UK-based study highlights susceptibility upto the third decade of life [22••].

Wood et al. [24••] along with a patient survey conducted a public survey sample of 1000 adults (≥18 years); 7.7 % described a past episode of an

anaphylactic reaction. Of these, 5.1 % had a probable and 1.6 % had very likely anaphylactic episodes on closer scrutiny. Food was the second commonest cause of anaphylaxis after medication.

As previously noted, medications are the commonest cause of fatal reactions in the adult population [1, 26•, 29, 30]. Food remains the most common cause of fatalities in individuals 19 years old or less [26•]. UK data showed vulnerability between 10 and 29 years of age with peanut and tree nuts causing 73 % of fatalities when the culprit food was identified [22••].

Adolescents and young adults are at greatest risk of fatality from anaphylaxis to peanuts and tree nuts [27•, 31]. There is a twofold increased risk in adolescents aged 14–17 years when compared to that in children aged 0–2 years, in a survey [32]. The cause of this higher rate in adolescents is speculated to be increased risk-taking behavior and decreased supervision by adults [21•, 27•].

FIA-related hospital admissions in US children have more than doubled during the decade 2000–2010 [33]. The incidence of recurrent food reactions needing reattendance at emergency department at paediatric hospitals in Stockholm was 9 per 100 patient-years [34]. Jerschow et al. reported that 52.4 % of deaths due to FIA occurred despite patients reaching emergency medical facilities [26•].

Specific foods as triggers

A large number (>170) of foods have been described as potential culprits for food reactions, although the vast majority of reactions are triggered by the 'eight major food allergens' [6]. The prevalence of specific food allergies varies among different age groups and geographic regions [6, 27•, 28••, 35]. Based on outcomes of food challenge to the eight major food allergens, the highest prevalence is of cow's milk allergy (0.6 %) with the lowest prevalence being wheat and shellfish allergy (equally 0.1 % for each) [34]. In contrast, the first reported data from the network of severe allergic reactions [28••] revealed peanut (17.2 %), wheat (8.9 %), hazelnut (8.1 %), hen's egg (6.9 %) and cow's milk (6.5 %) as the most frequent food elicitors for severe allergic reactions. Spices and additives caused severe allergic reactions less frequently [28••].

Rare and unusual cases

It is worth mentioning some reports of rare FIA cases. A case series of severe allergic reactions to lupin was published [36] suggesting that lupin is capable of causing severe reactions and that it is often omitted by food manufacturers from the ingredients list. A recent EU wide legislation enforceable by the European Food Standards Agency incorporates mandatory declaration of lupin among 14 allergens if present in the ingredients list of foods.

A case of anaphylaxis to peppermint was reported in a 69-year-old patient who was likely previously sensitized by peppermint plants he cultivated [37]. Sensitization through inhalation was also noted in a 20-year-old woman who had an anaphylactic reaction after ingestion of rabbit meat, known to have a history of allergy on exposure to rabbit; initially she was sensitized to rabbit epithelium and urine [38].

A 4-month-old baby developed an anaphylactic reaction to banana, becoming the youngest case of banana anaphylaxis [39]. Hidden food ingredients are thought to be the cause in some anaphylaxis cases previously characterized as idiopathic [40]. Hamilton et al. describe anaphylaxis in a 20-year-old milk allergic female after exposure to casein found in a kickboxing glove [41].

A useful paper for allergy practitioners listed food excipients in medications [42]; nonetheless, the risk appears to be excessively low as in most cases the quantity of the food allergen in drugs and vaccines cannot elicit an allergic reaction.

By definition, FIA is an immediate illness and rarely has the form of a biphasic or protracted reaction [43]. Commins et al. found basophil activation test corresponded with a positive food challenge test in patients with anaphylaxis to oligosaccharide alpha-1,3-galactose [44•]. In addition, it appears that there is a correlation between red meat allergy and B-negative blood groups [45]. Food challenge tests with purified palm tree profilin were used to prove profilin as a cause of severe food-mediated reactions in regions with high exposure to grass [46], despite the fact that oral allergy syndrome is the most common clinical presentation.

Risk factors and co-factors

Division of risk factors for FIA into three entities: (a) augmenting factors, (b) concomitant diseases and (c) cofactors has been suggested [47].

Menstruation is considered an augmenting factor [47], and this is supported by the increased female proportion in hospital admissions for FIA in individuals more than 15 years of age; in contrast, this proportion is inverted in children younger than 15 years [22••].

The role of female sex hormones and the mechanisms responsible are a subject under investigation [48••]; the authors of this study raise a considerable question on whether there should be caution with sex hormonal therapy and contraceptives in patients prone to anaphylaxis.

Underlying asthma and asthma severity have been associated with food-induced anaphylaxis [21•, 22••, 24••]. Turner et al. revealed that 75 % of fatalities from anaphylaxis had a diagnosis of asthma [22••].

Older people are at higher risk for death by anaphylaxis; this has been attributed to cardiovascular and respiratory comorbidities [49]. Nevertheless, in FIA, the risk is highest in adolescents [21•].

Beta-blockers or ACE inhibitors either as monotherapy or as combined treatment are suspected cofactors, although it is debated whether underlying cardiovascular disease and age are the true causes of anaphylaxis severity in this group. With the help of a mouse model, this hypothesis was examined and there is evidence that the above medications may affect mast cell responsiveness [50].

It is thought that peanut and tree nuts [22••, 27•, 31, 51], especially cashew nuts, [51] are frequently related to severe reactions.

Maternal diet [52, 53] and maternal atopy [54] likely linked to epigenetic changes have been related to development of food allergy and consequently to FIA. A study by Song et al. was able to demonstrate that offspring mice from peanut allergic mothers are at increased risk of having peanut allergy through an epigenetic alteration of the IL-4 gene promoter [54].

Incidence rate of food anaphylaxis and its cause varies in different geographical areas dependent on food habits, disease coding, use of databases and study design [21•, 28••]. A recent paper associated high latitude and low solar radiation with food-induced anaphylaxis in Chilean children. Vitamin D deficiency was the proposed mechanism [55].

Mechanisms

Interaction of food allergens and lipids has been studied by different groups, and it seems that lipids alter the action of food allergens in the gastrointestinal tract in terms of access to active immune sites of the gut-associated lymphoid tissue, passage through the intestinal epithelial protein-lipid complexes, degradation process etc. Lipids can also show immunomodulation and adjuvant actions or form protein-lipid complexes [56].

The role of plasma contact system in anaphylaxis has been investigated, and Sala-Cunill et al. showed that heparin-triggered activation of the bradykinin-forming contact system is significant in anaphylaxis. Increased plasma heparin levels, bradykinin formation and the intensity of contact system activation contribute to anaphylaxis severity [57]. The latter was also shown to be augmented by estrogen through increase of tissue expression of endothelial nitric oxide synthase (eNOS) that leads to enhanced vascular permeability according to findings from an experiment with an anaphylaxis mouse model [48••].

Prior to FIA, sensitization to the culprit food is required. Skin as a route of sensitization has been proposed and this is supported by several recent studies [58–60] demonstrating a correlation between fillagrin loss of function mutations, affected skin barrier and food allergy.

Impaired skin barrier leads to increased thymic stromal lymphopoietin (TSLP) expression and basophil infiltration, and it is likely that these promote intestinal allergic inflammation and risk for IgE-mediated food allergy [61].

Efforts have been made to further explore the role of FcγRIIb receptor and food-specific IgG antibodies to anaphylaxis and oral immunotherapy [62] and the contribution of eosinophils to gut immune homeostasis via activation of dendritic cells and migration to mesenteric lymph nodes [63].

Fish oil contains long-chain n-3 polyunsaturated fatty acids (n-3 LCPUFA) eicosapaentanoic acid (EPA) and docosahexaenoic acid (DHA), and it has been suggested it may prevent food allergy or atopy in children [64]. The involvement of Treg in tolerance induction by n-3 LCPUFA is under investigation, and van den Elsen et al. have shown that CD25+ Treg are crucial in preventing whey allergy in mice fed a fish oil diet [65].

Fasting can suppress immediate hypersensitivity reactions as shown in rat mast cells which had decreased degranulation activity [66].

Diagnosis

International guidelines for the diagnosis and management of anaphylaxis have been proposed [3, 11•]. Biomarkers such as serum tryptase have not always proved helpful for the diagnosis of food-induced anaphylaxis, as the levels are not usually raised, though there have been reports suggesting the opposite [67,

68]; nonetheless, serum tryptase results are available at a later time, hence unable to assist evaluation of the patients at their emergency department attendance and can only be used in order to confirm diagnosis.

Guidelines published in 2014 [12, 40] suggest considering use of component resolved diagnostic (CRD) tests [69] and the basophil activation test for clinical and research purposes, where personal history, skin prick tests and specific IgE tests are not conclusive. Use of the ISAC allergen array as an additional screening tool in cases of anaphylaxis of unknown cause might identify a culprit such as omega-5-gliadin or shrimp [70].

Careful interpretation of CRD results is required [68], given that clinical relevance of newly identified molecular allergens, such as the wheat component Tri a 36 [71], remains to be determined, especially for foods such as wheat where discrimination between allergy and sensitization is troublesome. Therefore, two studies from Northern Europe investigated wheat allergen components and confirmed that sensitization to gluten derived components [72, 73] is clinically relevant but also demonstrated the importance of dimeric alpha-amylase inhibitor 0.19 [72] for wheat allergy diagnosis. Additionally, a 9-kDa wheat lipid transfer protein was described as the culprit allergen in three cases of wheat-dependent exercise-induced anaphylaxis [74].

Peanut allergen components have been thoroughly investigated, and there is a consistency in results when searching the best predictors for clinical relevance [75, 76]. Interestingly, the use of fraction of exhaled nitric oxide (FeNO) was proposed as a safe non-invasive step of a diagnostic algorithm prior to blood collection for measuring specific IgE to Ara h 2, in order to distinguish children with peanut allergy from children tolerant to peanut all of which had a positive skin prick test to peanut with a mean wheal diameter between 3.0 and 8.9 mm [77].

The basophil activation test (BAT) has been added recently to the diagnostic tools for food allergy. BAT results were promising in an attempt to discriminate peanut allergic children from peanut sensitized children that tolerate peanut [78]. Basophil reactivity and sensitivity can provide additional information with regard to severity and thresholds of positive food challenges [79]. Limitations of BAT should be kept in mind, e.g., low or non-responders or its validity in allergic patients sensitized to other components [80].

Despite the progress of in vitro diagnosis, food provocation tests remain the gold standard for food allergy diagnosis. A positive result not only confirms diagnosis but more importantly can provide further clinical information and establish the threshold dose. However, even this invasive high risk and costly procedure may not be ideal: false-negative results [81], equivocal outcomes or questionable threshold levels have been reported [82•]. Food challenge symptom scoring may differ among physicians especially in the absence of objective symptoms [83]. Moreover, one could argue that challenge threshold outcomes do not represent real-life threshold levels, given that augmenting factors are lacking from a clinical setting and patients with severe or uncontrolled asthma or even patients with severe anaphylaxis are excluded from study protocols for ethical reasons. When defining the threshold dose, the time interval between increasing doses has been questioned as symptoms can manifest within 2 h after food ingestion, and to tackle this concern, Blumchen et al. suggested a modified prolonged food challenge protocol [82•]. Regardless, efforts have been made to determine the eliciting

dose for common food allergens and data were pooled from clinical and research food challenge trials. This allowed estimating doses that elicit reactions in 1 % of the allergic population (ED01) for peanut, cow's milk, egg and hazelnut [84••] and eliciting dose (ED10) for an allergic reaction in 10 % of the population for peanut, hazelnut, celery, fish and shrimp [85••]. These evidence-based reference doses can support food industry in developing a more consumer-friendly precautionary labeling.

Management, treatment, and prevention

Management/acute treatment

Understanding of allergen avoidance, access to adrenaline autoinjector and management plan are essential for the clinical management of acute reactions [3, 12, 40]. Unequivocally, intramuscular administration of adrenaline is the first line treatment for anaphylaxis and under no circumstances should not be considered as such. Early administration of adrenaline may prevent a fatal outcome [2, 3, 11•, 86]. Nevertheless, anaphylaxis is undertreated even in emergency department settings, and this reflects inadequate knowledge of medical personnel on anaphylaxis [23, 87–89]. The step prior to discharge, of two adrenaline autoinjectors prescription and an allergy referral, are often omitted [23, 24••, 87, 88]. Currently, there is more than one brand of autoinjector devices available in many EU countries. A comparison study between two of these highlighted the importance of regular reinforcement of their correct technique and indications for their use [90]. There is evidence that the needle length of the adrenaline autoinjectors may be a factor of insufficient delivery of adrenaline intramuscularly in a substantial proportion of food-allergic patients, especially females, with undesirable results [91]. On the contrary, there is risk of adrenaline administration into bone with the use of an autoinjector in children weighing less than 15 kg [92].

With no access to second-line management, the likelihood of a recurrent episode is high, though accidental reactions can occur even in patients who have been under the care of specialists [34]. Appropriate education on food avoidance and management of future reactions are key elements of long-term management strategies [12]. Patients, parents, and care takers can benefit from well-structured education programs [93] covering first-line treatment skills, food allergy management, psychological care and social interventions. Food allergy can have a big impact on patients' quality of life. Mothers of food-allergic children are likely to suffer with anxiety and stress [94] whilst adolescents reported an unpleasant impression of social isolation induced by their food allergy [95].

Raising social awareness may also protect this vulnerable group. Better overall understanding by restaurant staff with the help of training courses might add to the effort of risk minimization of allergic reactions in the community [96]. Another step further is education of the general public especially school and camp staff.

At the public health level, precautionary allergy labeling regulation in Europe has changed since December 2014 [14, 97] where clear and detailed information on the nature of the product or the substance that can trigger reaction should be provided on the label, whereas labeling will be extended to non-prepackaged food. However, the issue of allergens present in a food due

to cross-contamination remains unresolved and precautionary labeling statements (i.e. 'may contain' or 'trace amounts of') are confusing. Consequently, labeling issues have been linked to unexpected reactions and have led to restricted food selection for a considerable number of allergic consumers [84••, 98•]. More importantly, the actual risk of an allergic reaction due to allergen traces is not straightforward to calculate [98•].

Long-term treatment

Food allergy sufferers, clinicians and research groups envisage successful tolerance induction and maintenance with long-lasting effect. Effective treatments targeting immunomodulation are under development with allergen immunotherapy featuring promising results. Existing protocols are using different routes of administration, i.e. oral (OIT), sublingual (SLIT) and epicutaneous (EPIT), in addition to traditional subcutaneous immunotherapy. OIT has been used for milk, egg and peanut. Encouraging results from a randomized controlled two-phase trial that included a representative sample of UK peanut allergic children aged 7–15 years were recently published [99•]. Of the participants, 84 and 91 % developed tolerance of 800 μg of peanuts given daily in the first and second phase, respectively. Daily tolerance of five or even ten peanuts in some cases altered significantly patients' and their families' quality of life despite the presence of adverse reactions, mostly mild. It is not known whether discontinuation of treatment will result to loss of unresponsiveness. This was assessed by another study [100•] where children aged 1–16 years underwent a 5-year peanut OIT scheme. Treatment was discontinued, and 4 weeks later, subjects were challenged and the outcome was negative for 12 of 24 (50 %). Mechanisms of immunotherapy are still not known, and there are no predictive markers for successful treatment. However, in both OIT and SLIT reduced basophil reactivity and DC-driven T cell effector functions were observed [101]. Notably, immunological findings varied and even reversed throughout therapy and this might shed light to the reason behind failure of food immunotherapy to maintain unresponsiveness. For peanut allergy, OIT appears superior to SLIT at the expense of increased rate of adverse reactions [102].

Other immunomodulatory approaches are being explored such as the effectiveness of probiotic coadministration with immunotherapy [103], additional or separate treatment with antibodies [104, 105] and the role of distinct kinases in food allergy [104, 106]. Janus and Pim 1 kinase are part of the intracellular signaling pathway that generates cellular responses to stimuli from cytokines' and other receptors. It has been shown in mice that these kinases play a role in pathogenesis of food allergy, and their inhibition (e.g. use of ruxolitinib to inhibit Janus kinase) [104] may contribute to treatment and prevention of food allergy.

Prevention

'Prevention is better than cure' and various research projects are focused on primary prevention and try to determine whether allergen avoidance or a free diet is the best strategy during pregnancy, lactation period and infancy for food allergy prevention; so far, results are controversial. European guidelines for

primary prevention of food allergy collected and analyzed current evidence-based recommendations in order to provide useful and simple advice to families [13] as it appears that advice given from health care professionals about introduction of other potentially allergenic foods in the diet of children with pre-existing food allergy and their siblings varies radically [107].

A prospective cohort study from the USA assessed 616 participants and found that children (mean age 7.9 years) of mothers who had higher intake of peanut, milk and wheat during early pregnancy are less likely to present with allergy and asthma [23, 52].

More recently, a randomized open-label controlled trial from the UK (LEAP) demonstrated that early peanut consumption on a regular basis was associated with considerably lower frequency of peanut allergy compared to the group of full avoidance of peanut products in infants at high risk of peanut allergy [108••].

The role of maternal cow's milk avoidance during lactation was examined in a smaller sample (145 mother-infant pairs). The results suggested an association between cow's milk elimination from maternal diet, lower levels of mucosal specific IgA and the development of cow's milk allergy in infants [53].

Research needs

Better understanding of mechanisms of tolerance is necessary for designing both preventive and therapeutic interventions. It appears that food allergy immunotherapy is feasible; however, the protocols need to be optimized. Biomarkers able to predict the risk of anaphylaxis as well as helping its diagnosis are another unmet need.

Last, but not least, educational and public health programs are required to improve the quality of life of sufferers. Recently produced guidelines need to be kept systematically up-to-date and disseminated in order to raise social awareness and improve food safety.

Compliance with Ethics Guidelines

Conflict of Interest

Marina Tsoumani received travel grant and had accommodations expenses covered or reimbursed by EAACI. Vibha Sharma received travel grants and accommodation expenses to attend conferences from MEDA, ALK-abello, Stallergenes and has received grants on behalf of North West Paediatric Allergy and Network towards organising educational events from Allergy Therapeutics, Nutricia, GSK, Mead Johnson, Danone Abbott Nutrition and Nestle

Nikolaos G Papadopoulos has received funding for research from Nestle, MSD, GSK, has had consultant arrangements with AbbVie, Novartis, Menarini, MEDA, ALK-Abello, GSK, Chiesi, has received honoraria from Novartis, Uriach, GSK, Allergopharma, Stallergenes, MSD and has provided scientific advice to Abbvie, Sanofi, Menarini, MEDA

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors

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