

Highlights in nonhymenoptera anaphylaxis

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Purpose of review

The purpose of this review is to summarize new interesting findings in both research and clinical practice of nonhymenoptera anaphylaxis with particular emphasis on food and drug allergy.

Recent findings

Recent findings include some aspects of crossreactivity among betalactams, nonsteroidal anti-inflammatory drugs with special attention to an immunogenic metabolite of diclofenac and the mode of diclofenac-induced basophil degranulation. Also, new insights into the sometimes atypical anaphylaxis-like reactions after administration of monoclonal antibodies and the immunologic response to these molecules will be discussed, as well as the role of low-dose pholcodine exposure on the development of sensitization to neuromuscular blocking agents.

In food-related anaphylaxis, a significant increase of incidents has been observed over the last few years, especially among children of less than 5 years of age. Unfortunately, the severity of subsequent reactions cannot be predicted from the reaction history. Tree nuts and peanuts are the most important elicitors of fatal food-induced anaphylaxis.

Summary

In food-related anaphylaxis, prospectively evaluated marker allergens that are indicative of a potential anaphylactic reaction are still lacking. The drug groups covered in this review are of special interest either due to their prominent role as allergens or due to new findings.

Keywords

anaphylaxis, drug allergy, food allergy, monoclonal antibody

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Introduction

In 2001, European Academy of Allergology and Clinical Immunology (EAACI) published a rather broad definition of anaphylaxis with the aim of harmonizing the manifold meanings that have been attributed to this term [1]. In 2004, the World Allergy Organization (WAO) accepted this definition for global use [2]. On the basis of that definition, this review will cover new insights and developments in ‘severe, life-threatening, generalized or systemic hypersensitivity reactions caused by allergic, both immunoglobulin (Ig)E-mediated and non-IgE-mediated, or nonallergic mechanisms’, elicited by either food or drugs. In a review of 601 patients suffering from anaphylaxis – excluding cases resulting from Hymenoptera stings or immunotherapy – Webb and Lieberman [3] found food (22%) and medication (11%) to be the two most common elicitors of anaphylaxis apart from 59% of so-called idiopathic anaphylaxis cases. The survey done by Brown [4] of 1149 anaphylactic reactions of all origins

identified 22% drug-induced and 18% food-related anaphylaxes.

Comorbidities and cofactors

In an analysis of 25 patients suffering from fatal anaphylaxis [5^{*}], only two of 25 did not have one or more comorbidities. Eleven out of 25 patients had significant ischemic heart disease, other heart conditions were found in six, chronic obstructive pulmonary disease was identified in five, two had severe infections, and one patient had alcohol intoxication. These findings are in contrast with older studies, which stated lower frequencies of comorbidities. Preexisting cardiovascular disease and severe asthma are known risk factors for a fatal outcome of anaphylaxis [6], but have not been shown to be cofactors for the elicitation of anaphylaxis.

Sometimes the exposure to a single allergen is not enough to trigger anaphylaxis. The concomitant or

sequential exposure to a combination of allergens, infection, physical exercise, psychological stress, alcohol, menstruation [7] and/or concomitant medication is necessary to provoke a reaction [4] (summation anaphylaxis). This should be borne in mind if diagnostic means do not yield a definite eliciting allergen. The triggering combination of acetylsalicylic acid and allergen – with each single component not causing a reaction – is possibly not yet appreciated enough [7].

In exercise-induced anaphylaxis, the causative antigen and the pathophysiological mechanism have yet to be identified. In 1999, Ostrowski *et al.* [8] noted that strenuous exercise led to increased circulating levels of pro-inflammatory mediators, but simultaneously, cytokine inhibitors and anti-inflammatory cytokines restricted the magnitude and duration of the inflammatory response to exercise. In this context, Cooper *et al.* [9^{••}] propose an interesting hypothesis that this normally balanced immune/inflammatory response to exercise is disturbed by leukocytes that have been previously activated, for example by a food allergen, and are thereby rendered more responsive. When these food sensitized, gut-associated immune cells are released into the circulation as a result of exercise-associated blood redistribution, the interaction with larger numbers of immune cells including basophils and mast cells results in a systemic response [9^{••},10].

Probably the best-characterized subgroup of summation anaphylaxis is the separate entity of food-dependent exercise-induced anaphylaxis (FDEIA) [10]. Numerous foods have been implicated – wheat (ω -5-gliadin) being the single most important allergen [11[•],12,13] – that are usually tolerated if not followed by exercise. The anaphylactic symptoms are normally induced by physical exercise after food ingestion. Most reported cases have been triggered by strenuous exercise, but mild exercise and even exercise immediately before eating has also been reported. Apart from intake of allergenic food and many types of physical activity, additional triggering factors have appeared to play a role, such as drugs [nonsteroidal anti-inflammatory drug (NSAID), aspirin], alcohol, common cold, stress, and menstruation [10,11[•],14[•]].

Patients with cutaneous or systemic mastocytosis are also at an increased risk for anaphylaxis and possibly react more severely due to an excessive mast cell mediator release [15[•]].

The concept of cofactors that enhance or cotriggery anaphylaxis has especially been shown for anaphylaxis to food allergens, but is less well established in drug allergy. The severity of the reaction and its response to treatment may, however, be influenced by comedication with

β -blockers or other cardiotropic medications, although a clear function as cofactor in the elicitation of the anaphylactic reaction has not been demonstrated [16^{••}].

Highlights in food-induced anaphylaxis

To date, no reliable epidemiological data on the prevalence of food-induced anaphylaxis are available. A few years ago, a British investigation on hospital admission rates indicated an increase in the number of food allergy cases and patients with anaphylaxis over a period of 10 years [17].

Recently, in line with the British data, an Australian study on hospital admissions between 1993–1994 and 2004–2005 and deaths between 1997 and 2004 for anaphylaxis, angioedema and urticaria revealed a gradual increase for anaphylaxis of 8.8% per year. There was a particularly steep increase in the incidence of hospitalization for food-related anaphylaxis among children aged less than 5 years [18[•]]. Emergency department data from the National Electronic Injury Surveillance System (NEISS) predicted 2333 visits for food-induced anaphylaxis in the United States during a 2-month study period. The most frequently involved foods were shellfish in patients of at least 6 years of age, and egg, fruits, peanut and tree nuts in patients less than 6 years [19]. No food allergy induced deaths were reported during the study period. Two case series from the United States and the United Kingdom confirmed tree nuts and peanuts to be the most important elicitors of fatal-food-induced anaphylaxis [20[•],21]. More than 50% of fatalities occurred in patients with initially mild food-induced symptoms indicating that the severity of subsequent reactions cannot be predicted from the reaction history [20[•]]. Most importantly, to patients with mild food-induced symptoms epinephrine auto-injectors are usually not prescribed.

Patients with food allergy are advised to carefully read ingredient statements on packaged foods as a preventive measure. Increasingly, foods carry additional advisory labels such as ‘may contain’, indicating they may potentially contain a so-called hidden allergen. However, recent investigations also revealed that allergic consumers increasingly ignore such advisory labeling. Ten percent of investigated foods bearing an advisory statement in regard to peanut indeed contained peanut protein and 7% of foods to a clinical significant level [22]. This indicates that allergic consumers with peanut allergy do indeed take risks by ignoring advisory labels.

Allergen panels derived from various food sources allow us to define sensitization profiles in individual patients. This concept of ‘component resolved diagnosis’ (testing IgE reactivity by means of single allergenic molecules instead of allergen extracts that are mixtures of various

allergens) facilitates the correlation between sensitization to subpopulations of specific IgE and the clinical response. Sensitization to marker allergens have been described to be associated with more severe or even anaphylactic reactions, such as to the lipid transfer protein (LTP) in apple or cherry allergic patients [23,24], ω -5-gliadin in food dependent exercise-induced anaphylaxis and children with wheat allergy [12,13,25] or Cor a 9 in hazelnut allergic children [26]. Prospective studies including appropriate control groups that evaluate the relevance of sensitization to such marker allergens or even peptides with regard to the development of an anaphylactic reaction, however, are lacking.

Highlights in drug-induced anaphylaxis

Three conditions contribute to a complex variety of mechanisms of sensitization and allergic reaction: the diversity of allergenic molecules, most drugs acting as haptens and several types of immune response as described by Coombs and Gell. The following paragraphs highlight recent insights in the pathophysiology of anaphylactic reactions caused by some interesting drug groups.

Beta-lactam antibiotics

Antunez *et al.* [27] analyzed the in-vitro IgE crossreactivity in patients allergic to betalactams by investigating the specificity of IgE antibodies by means of radioallergosorbent (RAST)-inhibition tests. They found proof that IgE specificity is related to previous exposure to any betalactam and not necessarily to the eliciting betalactam, and that frequently IgE antibodies with different specificities could be found in the same patient. They found three types of sensitization patterns:

- (1) Isolated amoxicillin sensitizations with strong amoxicilloyl inhibition and positive skin tests only to amoxicillin.
- (2) Patients with comparable binding to benzylpenicilloyl and amoxicilloyl and crossreacting IgE antibodies to probably a single haptenic structure. These patients had positive skin tests to benzylpenicilloyl polylysine, minor determinant mixture and amoxicillin.
- (3) Benzylpenicilloyl sensitization despite a different beta-lactam elicitor of anaphylaxis, positive or negative skin tests to benzylpenicilloyl polylysine and negative skin tests to amoxicillin.

This study gives interesting clues and a new basis for establishing the clinical relevance in patients with anaphylaxis to a betalactam.

Nonsteroidal anti-inflammatory drugs

Berges-Gimeno and Martin-Lazaro explained the new classification and the management of NSAID-induced

reactions in a recent review [28]. It is mainly based on the differentiation between NSAID-induced urticaria and angioedema – either caused by a single drug or multiple NSAIDs, NSAID-induced asthma and rhinitis or anaphylaxis induced by a single NSAID. Especially with respect to the latter category, there have been several new findings. Naisbitt *et al.* [29**] saw a marked immune activation, as assessed in a murine lymph node assay, by a metabolite of diclofenac, 5'-hydroxyl diclofenac quinoneimine. Thus, an immunologically active metabolite of diclofenac was identified, although the attempt to measure T helper2-cytokines after stimulation with the metabolite was not successful, most likely due to methodological reasons. The study demonstrates that apart from the intolerance reactions elicited by the inhibition of the cyclooxygenase (COX)1 enzyme and the consequent increased arachidonic acid metabolism through the lipoxygenase pathway, there are also immunologic reactions to metabolites of the ingested drug.

Another interesting feature of diclofenac hypersensitivity has been described by Malbran *et al.* [30*]. In contrast to the rapid and massive extrusion of granules to the extracellular milieu by basophils in IgE-mediated anaphylaxis, basophils from diclofenac-sensitized patients possibly undergo a form of fractionated degranulation. This fractionated or 'piecemeal' degranulation does not lead to granule-plasma membrane fusion and thereby does not increase CD63 expression on the surface of the basophils, as assessed with the Basophil activation test (BAT) [30*]. Malbran *et al.* stimulated the basophils with diclofenac. It would be interesting to see which type of degranulation occurs after stimulation with an immunogenic metabolite.

Monoclonal antibodies

With soaring development and application of recombinant chimeric or humanized monoclonal antibodies (mAb) in many different diseases, hypersensitive reactions including anaphylaxis are reported with increasing frequency and in some cases an unusual course is undertaken challenging some traditional concepts of anaphylaxis. Anaphylactic reactions are most common to mouse mAbs, followed by chimeric mAbs (~75% human), humanized (~90% human) and human mAbs. It usually occurs within 4 h after the first or any subsequent administration of the drug. In some patients, IgE against an idiotypic, allotypic or murine portion of the mAb has been identified [31,32*,33]. In others, IgG might be involved [32*]. It is often difficult to distinguish true anaphylactic reactions from the rather frequent monosymptomatic or oligosymptomatic infusion reactions presenting as malaise, hypotension or difficulty in breathing that are commonly attributed to therapy-induced cytokine release or from serum sickness like symptoms.

In cetuximab [chimeric mAb type IgG1 against epidermal growth factor receptor (EGFR) used for colorectal carcinomas], anaphylaxis occurs in about 5% of patients, usually during the first infusion and can be severe in 50% [34]. It has been found to be caused by preexisting IgE antibodies to the oligosaccharide galactose- α -1,3-galactose, a posttranslational modification on cetuximab [32[•]]. This epitope is expressed on tissues of all mammals except humans and old-world primates [35] who develop natural antibodies. Gemtuzumab, a humanized mAb with a covalently bound bacterial toxin used for CD33-positive acute myeloid leukemia, also occasionally causes severe anaphylaxis [34,36]. It is not known so far whether the antigen is some structure on the mAb or on the toxin. Ibritumomab, a mouse IgG1 mAb bound to radioactively labeled tiuxetan, and tosituzumab, another radioactively labeled mouse mAb, are used in the treatment of pretreated, relapsed CD20 positive nonHodgkin lymphoma. Human antimouse antibody (HAMA) formation has been demonstrated in these patients in 2 and 17% [37[•]], respectively, who were heavily pretreated with other cytostatic treatments and therefore immunocompromised. HAMA-formation seems to be linked to an increased risk for severe anaphylaxis [34]. In contrast, HAMA formation in previously untreated patients receiving tosituzumab as single agent occurs in 63% [37[•]], causing a higher incidence of anaphylaxis.

Anaphylactic reactions during or after the first or subsequent administration of rituximab (chimeric IgG1 mAb against CD20) or trastuzumab (chimeric IgG1 mAb against the HER2-protein) occur relatively frequently, but are rarely severe [34].

The recently revised product information sheet (black box warning) of omalizumab (humanized mAbs type IgG1 against Fc-region of IgE) warns that approximately 0.2% of treated patients experienced anaphylaxis. The causative antigen is yet to be defined. Possible mechanisms are anti-allotypic or anti-idiotypic antibodies (IgE or IgG) that are either preexisting or develop after exposure [32[•]]. On the contrary, Price and Hamilton [38] described two patients who experienced anaphylactic reactions to a polysorbate (Tween 80) in the omalizumab preparation, a known histamine-releasing agent [39].

Delayed onset anaphylaxis (>2 h to several days with protracted course of symptoms over several hours) is not uncommon for several mAb therapeutics including omalizumab, infliximab, trastuzumab, daclizumab, basiliximab and gemtuzumab ozogamicin [40^{••}]. This may in part be due to the pharmacokinetic profiles, for example, omalizumab reaching peak serum concentrations after subcutaneous injection on average after 7–8 days, although the reason for these long delay periods is not understood so far.

The chimeric mAb infliximab against TNF α is a known elicitor of acute and delayed infusion reactions, occurring in approximately 5–10% of all infusions [31]. Despite methodological limitations in the analysis of serum for infliximab levels and levels of antibodies to infliximab (ATI), Baert *et al.* [41] clearly demonstrated that the development of ATI occurred in 61% of all patients in their cohort of Crohn's Disease after five infusions, and that the ATI-serum concentrations were significantly lower in patients with concomitant immunosuppressive therapy. Also, ATI correlated with an increased risk of anaphylactic infusion reactions and shorter duration of response was due to lower infliximab concentrations. Farrell *et al.* [42] showed that intravenous hydrocortisone premedication reduces ATI levels but is not able to prevent ATI formation or infusion reactions. Augustsson *et al.* [43^{••}] demonstrated a clear protective effect of daily low-dose oral prednisone, which resulted in a reduction in the risk for an infusion reaction by about half in a cohort of patients with rheumatoid arthritis and an overall marked, although unexplained decrease in the frequency of treatment-limiting infusion reactions since 2000.

Neuromuscular blocking agents

Anaphylaxis to neuromuscular blocking agents (NMBAs) has been attributed to IgE-mediated sensitization toward a quaternary ammonium ion (QAI) epitope, which NMBA share with many common drugs and chemicals, for example morphine. This may explain the fact that many reactions to NMBA occur on first known exposure [44]. An interesting aspect is that the reported frequency of anaphylaxis varies greatly between different countries. For instance, the sensitization to QAI is six times higher in Norway than in Sweden [45]. Also in France very high sensitization rates have been reported previously [46,47]. This 'French paradoxon' has so far not been clearly explained. In a recent evaluation of two individuals without history of anaphylaxis during anesthesia, pholcodine, a common, QAI containing ingredient of OTC cough syrup marketed in Norway but not in Sweden, has been shown to stimulate synthesis of total IgE and specific IgE to pholcodine, morphine and suxamethonium [48]. Harboe *et al.* [49[•]] then exposed 17 patients with previously diagnosed IgE-mediated anaphylaxis to a NMBA for 1 week daily with a cough syrup with or without pholcodine. Total IgE and specific IgE to morphine, suxamethonium and pholcodine were measured before and 4 and 8 weeks after the exposure. The group receiving pholcodine-containing syrup responded with a remarkable and statistically highly significant increase in total IgE and specific IgE to pholcodine, morphine and suxamethonium. Pholcodine sensitization, however, is not a direct predictor for QAI sensitization, as an additional allergenic epitope, not crossreacting with the QAI has been found [45]. Still, the IgE sensitization to QAI seems

to be related to pholcodine exposure, which might therefore be a risk factor for NMBA anaphylaxis. There is need for a study to establish pholcodine as the actual primary sensitizer. In this light, a more cautious access to pholcodine seems reasonable [49*].

Future perspectives

Detailed knowledge on eliciting allergens and their mode of action and a deeper insight into the mechanisms of anaphylaxis will improve patient management.

Conclusion

Analyses of hospital admission rates indicate that severe allergic reactions to foods are increasing. Most importantly, food-induced fatalities are often preceded by mild-allergic reactions. Prospectively evaluable marker allergens that are indicative for a potential anaphylactic reaction are still lacking.

Interesting new findings and observations for several drug groups have been outlined: new aspects of IgE crossreactivity in betalactams, considerations of a possible antigen in diclofenac hypersensitivity and the mode of diclofenac-induced degranulation of basophils. Frequent reactions to monoclonal antibodies that may be IgE-mediated or caused by cytokine release but are nevertheless difficult to distinguish, the interesting aspect of pholcodine sensitization and its possible role in anaphylactic reactions to neuromuscular blocking agents have also been presented.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 365–366).

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