Symposium on the Definition and Management of Anaphylaxis: Summary report

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Abbreviations used
ED: Emergency department
EIA: Exercise-induced anaphylaxis
FAAN: Food Allergy and Anaphylaxis Network
FDA: Food and Drug Administration
NIAID: National Institute of Allergy and Infectious Diseases

The phenomenon of anaphylaxis was first described in the scientific literature about 100 years ago by Portier and Richet,[1] who reported that their attempts to immunize dogs against the sting of jellyfish with *Actinia* extract instead brought about an acute anaphylactic episode.[1,2] In the extreme or classic form, anaphylaxis typically involves the cutaneous, respiratory, cardiovascular, and gastrointestinal systems, target organs all heavily populated with mast cells. Although medical practitioners can readily recognize such typical forms of anaphylaxis, its presentation is often more enigmatic, with variable target organ involvement and expression of symptoms. A perusal of various textbooks and reviews on the topic indicates that there is no consensus on exactly how to define anaphylaxis, and consequently, there is considerable disagreement about its prevalence, diagnosis, and management. In April 2004, the National Institute of Allergy and Infectious Diseases (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) cosponsored a multidisciplinary Symposium on the Definition and Management of Anaphylaxis to bring together experts from various disciplines that deal with anaphylaxis. The goal was to review current knowledge and to discuss a definition, treatment strategies, and research objectives.

This 2-day meeting brought together experts and representatives of 12 other professional, governmental, and lay organizations. Organizations represented at the NIAID/FAAN Symposium included the American Academy of Allergy, Asthma and Immunology; the American Academy of Family Physicians; the American Academy of Pediatrics; the American College of Allergy,

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Asthma and Immunology; the American College of Emergency Physicians; the American Society of Anesthesiologists; the Centers for Disease Control and Prevention; the Food Allergy Initiative; the International Life Sciences Institute; the National Association of EMS Physicians; the Society for Academic Emergency Medicine; and the US Food and Drug Administration (FDA). The meeting provided an opportunity for attendees to exchange information, gain a better perspective of how anaphylaxis is recognized and treated, find commonalities between the various specialities' approaches, and identify future research needs. The information presented in this article serves as a basis for future development of a clinical definition of anaphylaxis and a management strategy, and for expansion of a research agenda.

In 1998, a Joint Task Force on Practice Parameters[3] defined *anaphylaxis* as an ''immediate systemic reaction caused by rapid, IgE-mediated immune release of potent mediators from tissue mast cells and peripheral basophils.'' The most common etiologies of anaphylactic reactions include allergic responses to food, medications, *Hymenoptera* stings, and latex. Mechanistically, anaphylactic reactions are distinguished from *anaphylactoid reactions*, which ''mimic signs and symptoms of anaphylaxis, but are caused by non-IgE-mediated release of potent mediators from mast cells and basophils.'' Although they provide a mechanistic concept of anaphylaxis, these definitions are of marginal utility to the physician, emergency personnel, and other health care personnel faced with the diagnosis and treatment of a patient presenting with any of a variable constellation of signs and symptoms of this disorder.

One of the major challenges in the study of anaphylaxis is the lack of a widely accepted standard working definition.[4-6] In general, published studies use definitions that incorporate various signs and symptoms of anaphylaxis and specific intervals between allergen exposure and the clinical reaction, but specific elements of the definitions vary.[6-12] One of the major consequences of this lack of standard definition is the failure to diagnose anaphylaxis consistently, as pointed out in several studies.[6,8,13] In a review of 19,122 emergency department (ED) visits,[8] 17 cases of anaphylaxis were identified, but only 4 had been appropriately diagnosed and coded. This lack of a consistent definition contributes to the wide variation in the management of anaphylaxis seen in North American EDs.[14]

EPIDEMIOLOGY AND INTERNATIONAL CLASSIFICATION OF DISEASES CODING

Study of the epidemiology of anaphylaxis has been hampered by lack of an agreed-on definition and a lack of required reporting of either fatal or serious events. A failure to agree on how severe a reaction must be to code it *anaphylaxis* as opposed to an *allergic reaction* and to appreciate the variable presentation of anaphylaxis contributes to the problem. Very few population-based studies have been attempted, so the actual incidence of anaphylaxis remains uncertain. Estimates of the incidence range from 10 to 20/100,000 population per year.[6,12,15] In 2003, the new codes of the International Classification of Diseases, Tenth Revision, were put in place to describe fatal anaphylactic reactions, such as ''anaphylactic shock due to adverse food reaction'' (T78.0) and ''anaphylactic shock, unspecified'' (T78.2). However, data presented at the symposium indicated that these codes are underused. Until there are universally accepted diagnostic criteria, standardized coding, and reporting of anaphylaxis, the true incidence and lifetime prevalence of anaphylaxis will remain unknown.

IMMUNOLOGY OF ANAPHYLAXIS

Aggregation of FcεRI by allergen-driven cross-linking of receptor-bound IgE activates mast cells and basophils to release mediators that induce the pathophysiologic features of the anaphylactic response.[16] Initial sensitization occurs through a highly coordinated series of steps involving a variety of cell types and mediators,[17] which is affected by environmental exposure and complex genetic factors. Consequently, even identical twins raised together may lack complete clinical concordance (eg, peanut allergy: monozygotic twins, 64%, compared with dizygotic twins, 7%),[18] thereby highlighting the inaccuracy of making genetic predictions for any one individual, but recognizing the significant genetic component to allergic disease.

An important immunologic feature of allergy is the fact that not all sensitized subjects exhibit clinical reactivity. Although the quantity of circulating IgE antibodies to both food and airborne allergens appears to correlate directly with the probability of clinical reactivity,[19-21] the exact series of events that occur between contact with an allergen by a sensitized individual, and sufficient activation of mast cells, basophils, and possibly other cells to induce an anaphylactic reaction, remains to be elucidated. When mast cells/basophils are activated, several well-characterized mediators are released (eg, histamine and tryptase). Unfortunately, tryptase is not found to be elevated consistently in the blood of patients presenting with anaphylaxis,[22] especially in food allergy,[23] and histamine is elevated only briefly at the outset of the reaction and is unstable to routine handling. Therefore, additional biomarkers need to be identified that are both present during most or all anaphylactic reactions and easily and rapidly measured.

PATHOPHYSIOLOGY OF ANAPHYLAXIS

Allergic reactions begin when an allergen crosses an epithelial and/or endothelial barrier and then interacts with cell-bound IgE antibodies. The integrity of natural barriers such as the skin or the gastrointestinal tract must be breached, and these allergens must then gain access to the reactive, sensitized cells in tissues (mast cells) or blood