Anaphylaxis

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Anaphylaxis is an acute multi-system severe type I hypersensitivity reaction. The term comes from the Greek words ἀνά (against) and φύλαξ (protection).[1]

Due in part to the variety of definitions, between 1% and 15% of the population of the United States can be considered "at risk" for having an anaphylactic reaction if they are exposed to one or more allergens. Of those people who actually experience anaphylaxis, up to 1% may die as a result. Anaphylaxis results in approximately 1,500 deaths per year in the U.S.[3][4] In England, mortality rates for anaphylaxis have been reported as up to 0.05 per 100,000 population, or around 10-20 a year.[5] Anaphylactic reactions requiring hospital treatment appear to be increasing, with authorities in England reporting a threefold increase between 1994 and 2004.[6]

Based on the pathophysiology, anaphylaxis can be divided into "true anaphylaxis" and "pseudo-anaphylaxis" or "anaphylactoid reaction." The symptoms, treatment, and risk of death are the same; however, "true" anaphylaxis is caused by degranulation of mast cells or basophils mediated by immunoglobulin E (IgE), and pseudo-anaphylaxis occurs without IgE mediation.[7]

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Classification

Biphasic anaphylaxis

Biphasic anaphylaxis is the recurrence of symptoms within 72 hours with no further exposure to the allergen. It occurs in between 1–20% of cases depending on the study examined.\[8\] It is managed in the same manner as anaphylaxis.\[9\]

Anaphylactic shock

Anaphylactic shock is anaphylaxis associated with systemic vasodilation which results in low blood pressure. It is also associated with severe bronchoconstriction to the point where the individual is unable to breathe.

Pseudoanaphylaxis

Main article: Pseudoanaphylaxis

The presentation and treatment of pseudoanaphylaxis is similar to that of anaphylaxis. It however does not involve an allergic reaction but is due to direct mast cell degranulation.\[10\] This can result from morphine, radiocontrast, aspirin and muscle relaxants.\[11\]

Active anaphylaxis

Active anaphylaxis is what is naturally observed. Two weeks or so after an animal, including humans, is exposed to certain allergens, active anaphylaxis (which is simply called "anaphylaxis") would be elicited upon exposure to the same allergens.

Passive anaphylaxis

Passive anaphylaxis is induced in native animals which receive transfer of the serum experimentally from
sensitized animals with certain allergens. Passive anaphylaxis would be provoked in the recipient animals after exposure to the same allergens.\(^{[12]}\)

## Signs and symptoms

Anaphylaxis can present with many different symptoms due to the systemic effects of histamine release.\(^{[13]}\) These usually develop over minutes to hours.\(^{[9]}\) The most common areas affected include: skin (80% to 90%), respiratory (70%), gastrointestinal (30% to 45%), heart and vasculature (10% to 45%), and central nervous system (10% to 15%).\(^{[9]}\)

### Skin

Skin involvement may include generalized hives, itchiness, flushing, and swelling of the lips, tongue or throat.\(^{[14]}\)

### Respiratory

Respiratory symptoms may include shortness of breath, wheezes or stridor, and low oxygen.\(^{[14]}\)

### Gastrointestinal

Gastrointestinal symptoms may include crampy abdominal pain, diarrhea, and vomiting.\(^{[14]}\)

### Cardiovascular

Due to the presence of histamine releasing cells in the heart coronary artery spasm may occur with subsequent myocardial infarction or dysrhythmia.\(^{[9]}\)

### Nervous system

A drop in blood pressure may result in a feeling of lightheadedness and loss of consciousness. There may be a loss of bladder control and muscle tone,\(^{[14]}\) and a feeling of anxiety and "impending doom".\(^{[15]}\)

## Causes

Anaphylaxis can occur in response to any allergen. Common triggers include insect bites or stings, foods, medication and latex rubber.\(^{[16]}\)

### Food

Many foods can trigger anaphylaxis. The most common are peanut, tree nuts, shellfish, fish, milk, and egg. Severe cases are usually the result of ingesting the allergen.\(^{[9]}\)

### Medication

Any medication may potentially trigger anaphylaxis. The most common to do so include antibiotics (β-lactam...
antibiotics in particular), aspirin, ibuprofen, and other analgesics. Some drugs (polymyxin, morphine, x-ray contrast and others) may cause an "anaphylactoid" reaction (anaphylactic-like reaction) on the first exposure. This is usually due to a toxic reaction, rather than the immune system mechanism that occurs with "true" anaphylaxis. The symptoms, risk for complications without treatment, and treatment are the same, however, for both types of reactions. Some vaccinations are also known to cause "anaphylactoid" reactions.

**Venom**

Venom from stinging or biting insects such as Hymenoptera or Hemiptera may induce anaphylaxis in susceptible people.

**Pathophysiology**

Anaphylaxis is a severe, whole-body allergic reaction. After an initial exposure "sensitizing dose" to a substance like bee sting toxin, the person's immune system becomes sensitized to that allergen. On a subsequent exposure "shocking dose", an allergic reaction occurs. This reaction is sudden, severe, and involves the whole body.

Classified as a type I hypersensitivity, anaphylaxis is triggered when an antigen binds to IgE antibodies on mast cells based in connective tissue throughout the body, which leads to degranulation of the mast cells (the release of inflammatory mediators). These immune mediators cause many symptoms, including common symptoms of allergic reactions, such as itching, hives, and swelling. Anaphylactic shock is an allergic reaction to an antigen that causes circulatory collapse and suffocation due to bronchial and tracheal swelling.

Different classes of antibodies are produced by B cells to bind and destroy substances that the immune system has identified as potentially dangerous pathogens. Each B cell produces thousands of identical antibodies that can attack a single, small part of a pathogen. In susceptible individuals, antibodies may be produced against innocuous antigens or allergens, such as components of common foods or plants. One class, the IgE antibodies, can trigger anaphylaxis. Production of IgE antibodies may persist for months, even in the complete absence of the allergen. These IgE antibodies associate with a receptor on the surface of mast cells. If the antibody binds to its specific antigen, then the antibody triggers degranulation of the mast cell.

Mast cells become the major effector cells for immediate hypersensitivity and chronic allergic reactions.

Mast cells are large cells found in particularly high concentrations in vascularized connective tissues just beneath epithelial surfaces, including the submucosal tissues of the gastrointestinal and respiratory tracts, and the dermis that lies just below the surface of the skin. They contain large granules that store a variety of mediator molecules including the vasoactive amine, histamine. Histamine causes dilation of local blood vessels and smooth-muscle contraction. Other molecules in the mast cell granules include lipid inflammatory mediators such as prostaglandin D2 and leukotriene C4 as well as tumor necrosis factor-α (TNF-α), a cytokine. The importance of TNF-α is most noted in the activation of the endothelium. TNF-α, the prototype of the TNF family cytokines, can induce endothelial cells to present E-selectin and ICAM-1, both of which are cell adhesion molecules (CAM) that mediate the "roll and stick" mechanism of leukocyte extravasation, termed diapedesis. While this process is essential for the recruit of leukocytes to a localized area during an inflammatory response, it can be catastrophic in cases of systemic infection. Point in case, the presence of said infection in the bloodstream, or sepsis, is accompanied by the release of TNF-α by macrophages in liver, spleen, and other systemic sites. The systemic release of TNF-α causes vasodilatation, which leads to a loss of blood pressure and increased vascular permeability, leading to a loss of plasma volume and eventually to shock.
TNF-α, along with the other aforementioned mast cell granule contents become exocytosed upon activation of the mast cell. Activation is achieved only when IgE, bound to the high-affinity Fcε receptors (FcεR1), are cross-linked by multivalent antigen. The FcεR1 is a tetrameric receptor composed of a single α chain, responsible for binding the IgE, associated with a single β chain and a disulfide linked homodimer of γ chains that initiate the cell signal pathway. Once the FcεR1 are aggregated by the cross-linking process, the immunoreceptor tyrosine-based activation motifs (ITAMs) in both the β and γ chains are phosphorylated by LYN, a protein tyrosine kinase (PTK) belonging to the Src family. The ITAM domain is simply a conserved sequence motif generally composed of two YXXL/I sequences separated by about six to nine amino acids, where Y is tyrosine, L is leucine, I isoleucine and X any amino acid. Their phosphorylation in the β and γ chains provide high-affinity docking sites for the SH2 domains of additional LYN and the SYK (spleen tyrosine kinase), respectively. These SH2 domains (Src homology 2 domain) are found in a numerous cell-signaling proteins and bind to phosphotyrosine through a very specific sequence. As the signal continues to propagate through the pathway, the membrane bound molecule, named linker for activation of T cells (LAT), is phosphorylated by the LYN and SYK and acts as a scaffold protein, organizing other molecules that complete the degranulation of mast cells, as well as promote further cytokine production. The most notable of these LAT affected molecules is Phospholipase C (PLC). As in many cell signaling pathways PLC hydrolyzes the phosphodiester bond in phosphoatidylinositol-4,5-bisphosphate [PI(4,5)P2] to yield diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP3). A well-characterized second messenger, IP3, signals the release of calcium from the endoplasmic reticulum. The influx of cytosolic Ca2+ and phosphoatidylserine further activates Phosphokinase C (PKC) bound to DAG. Together, it is the cytosolic Ca2+ and PKC signal the degranulation of the mast cell.

Although less well mapped, similarly prevailing cell signaling molecules, such as Ras, a monomeric G protein, SOS (son of sevenless homologue) and MAPK (mitogen-activated protein kinase) lead to the upregulation of cytokines and the previously mentioned eicosanoids, prostaglandin D2 and leukotriene C4.

While this cell single pathway is sufficient to induce degranulation, it is not the only effective mechanism. Studies with LYN deficient mice have shown that degranulation is still inducible. Consequently, several alternative pathways leading to mast cell degranulation have been mapped. The first of which, dubbed the “complementary” pathway, determined that the crosstalk between LYN and another Src family PTK, called FYN, is an essential interaction to degranulation, along with the preferential activity of Phosphotidylinositol 3-kinase (PI-3K) over PLC. Studies have also elucidated subsequent pathways that utilize the integration of G-protein-coupled receptors to mediate the degranulation and cytokine production mechanism of activated mast cells.

IgE binding to FcεR1 in the absence of a specific antigen still induces the up-regulation of FcεR1 surface expression in mast cells through autocrine signaling of cytokines. However, not all IgE are equally capable of inducing such as secretion. Therefore, researchers have divided all invariant IgEs into two major categories: highly cytokinergic (HC), where the production and secretion of various cytokines and other activation events including degranulation is inducible, and poorly cytokinergic (PC) in which no autocrine signaling is observed. The former, HC IgE, brings forward a reaction in which cytokines are exocytosed and act as autocrine and paracrine signaling molecules. As such, mast cells with bound HC IgE attract other mast cells even in the absence of antigen crosslinking. While the exact structural features that account for the function differences between HC and PC IgE has yet to be determined their effects are thought to be the result of intracellular cell signaling. IgE binding to FcεR1 leads to a greater stability of the mast cell and increased production of surface receptors. The newly expressed FcεR1 then aggregate on the surface, independent of antigen binding. The cell signaling pathway then initiates and appears to involve components used in the alternative mechanisms. Mast cell migration is dependent on soluble factors such as adenosine, leukotriene B4 and other chemokines, whose secretion is dependent upon the activity of LYN and SYK. The degranulation of mast cells in the absence of antigen crosslinking...
of antigen, can then be initiated by G-protein-couple receptors (GPCR) stimulated by soluble factors agonists and completed by downstream activity of PI3K.[21]

**Diagnosis**

Anaphylaxis is diagnosed with high likelihood based on clinical criteria. These criteria are fulfilled when any one of the following three is true:[14]

1. Symptom onset within minutes to several hours of allergen exposure with involvement of the skin or mucosal tissue and any of the following: hives, itchiness, or swelling of the airway; plus either respiratory difficulty or a low blood pressure.
2. Any two or more of the following symptoms within minutes to several hours of allergen exposure: a. Involvement of the skin or mucosa b. Respiratory difficulties c. Low blood pressure d. Gastrointestinal symptoms
3. Low blood pressure within minutes to several hours after exposure to known allergen

Apart from its clinical features, blood tests for tryptase (released from mast cells) might be useful in diagnosing anaphylaxis.[25]

Allergy testing may help in determining what triggered the anaphylaxis. In this setting, skin allergy testing (with or without patch testing) or RAST blood tests can sometimes identify the cause.

**Prevention**

Immunotherapy with Hymenoptera venoms is effective against allergies to bees, wasps, hornets, yellow jackets, white faced hornets, and fire ants.[26]

The greatest success with prevention of anaphylaxis has been the use of allergy injections to prevent recurrence of sting allergy. The risk to an individual from a particular species of insect depends on complex interactions between likelihood of human contact, insect aggression, efficiency of the venom delivery apparatus, and venom allergenicity. Venom immunotherapy reduces risk of systemic reactions below 3%. [citation needed] One simple method of venom extraction has been electrical stimulation to obtain venom, instead of dissecting the venom sac.

A potential vaccine has been developed to prevent anaphylaxis due to peanut and tree nut allergies if they are exposed to a small amount of peanuts or nuts. Although it shows some promise to reduce the likelihood of anaphylaxis in affected individuals, the vaccine has not yet been approved for marketing and distribution.[27] Desensitization techniques are also being studied for peanut allergies.[28]

**Management**

Anaphylaxis is a medical emergency which may require resuscitation measures such as airway management, supplemental oxygen, large volumes of intravenous fluids, and close monitoring.[9] Administration of epinephrine is the treatment of choice with antihistamines and steroids often used as adjuncts. A period of in hospital observation for between 6 and 24 hours is recommended for people once they have returned to normal due to concerns of biphasic anaphylaxis.[8][29]
Epinephrine

Epinephrine (adrenaline) is the primary treatment for anaphylaxis with no absolute contraindication to its use.\[9\] Epinephrine improves airway patency, improves blood pressure, and may be life-saving. The recommended dose is 500 µg (or 0.5 mL adrenaline injection 1 in 1000) given intramuscularly.\[30\] A dose of 300 µg (0.3 mL adrenaline injection 1 in 1000) may be appropriate for immediate self-administration.\[30\] The dose is repeated if necessary at 5-minute intervals according to blood pressure, pulse and respiratory function.\[30\] If necessary, it can also be given intravenously using dilute solution.\[30\] Epinephrine autoinjector is provided for self-prescription.

Intravenous fluids

Anaphylaxis can lead to massive losses of intravascular fluids. Thus large amounts of intravenous fluids maybe required.\[29\]

Adjuncts

Antihistamines

Antihistamines while commonly used and assumed effective based on theoretical reasoning are poorly supported by evidence. A 2007 Cochrane review did not find any good quality studies upon which to base recommendations.\[31\]

Steroids

Corticosteroids, are unlikely to make a difference in the current episode of anaphylaxis, but may be used in the hope of decreasing the risk of biphasic anaphylaxis. How effective they are at achieving this, however, is uncertain.\[8\]

Preparedness

People prone to anaphylaxis are advised to have an "allergy action plan", and parents are advised to inform schools, etc., of their children's allergies and what to do in case of an anaphylactic emergency.\[32\] The action plan usually includes use of epinephrine auto-injectors, the recommendation to wear a medical alert bracelet, and counseling on avoidance of triggers.\[33\] Immunotherapy is available for certain triggers to prevent future episodes of anaphylaxis. A multi–year course of subcutaneous desensitization has been found effective against stinging insects while oral desensitization is effective for many foods.\[9\]

Epidemiology

The rate of anaphylaxis appears to be increasing. The rate in the 1980s was 21 per 100,000 per year while in the 1990s it had increased to 50 per 100,000 per year.\[9\] The risk is greatest in young people and females. The trigger in the young is usually food related while in adults, medications and insect venoms are more common causes.\[9\]

Due in part to the variety of definitions, between 1% and 15% of the population of the United States can be considered "at risk" for having an anaphylactic reaction if they are exposed to one or more allergens, especially
penicillin and insect stings. Most of these people successfully avoid their allergens and will never experience anaphylaxis. Of those people who actually experience anaphylaxis, up to 1% may die as a result.[2] Anaphylaxis results in approximately 1,500 deaths per year in the U.S.[3] (one out of every 1,600 of the 2.4 million deaths from all causes each year in the U.S.;[4]). The most common presentation includes sudden cardiovascular collapse (88% of reported cases of severe anaphylaxis). In England, mortality rates for anaphylaxis have been reported as up to 0.05 per 100,000 population, or around 10-20 a year.[5] Anaphylactic reactions requiring hospital treatment appear to be increasing, with authorities in England reporting a threefold increase between 1994 and 2004.[34]

References


External links

- Anaphylaxis information (http://www.aaaai.org/patients/publicedmat/tips/whatisanaphylaxis.stm) from the American Academy of Allergy and Immunology
- Patient information: Anaphylaxis (http://www.uptodate.com/patients/content/topic.do?topicKey=55pia.nJGQ/Gs) from UpToDate
- Emergency treatment of anaphylactic reactions (http://www.resus.org.uk/pages/reaction.pdf) - Resuscitation Council (UK)

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