Anaphylaxis

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Abstract

Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction. The pathophysiology of anaphylaxis can be described as immunologic and non-immunologic. Classification can be based on the time course of the anaphylactic reaction which may be uniphasic, biphasic or protracted. There are many triggers for anaphylaxis; the most commonly identified are food, drugs and venom. Perioperative anaphylaxis is a serious complication reported in up to 1 in 13,000 anaesthetics. It can be caused by neuromuscular blocking agents (NMBAs), antibiotics, blood and blood products, dyes, chlorhexidine and natural rubber latex. The presence of other comorbidities and concurrent medications impacts on the severity of symptoms and the response to treatment in patients with anaphylaxis. The diagnosis of anaphylaxis is mostly clinical; however it can be supported by various laboratory tests like serum tryptase levels, plasma histamine levels and the mature β-tryptase levels. The basic principles of management of anaphylaxis are the same in all age groups. The use of the Resuscitation Council Anaphylaxis Algorithm aids in the recognition and treatment of an anaphylactic reaction.

Keywords β-Tryptase; biphasic anaphylaxis; pathophysiology of anaphylaxis; plasma histamine; tryptase; uniphasic

Royal College of Anaesthetists CPD Matrix: 1BO1, 2A06, 2C04

Learning objectives

After reading this article, you should be able to:

- define and classify anaphylaxis
- describe the pathophysiology of anaphylaxis
- understand the diagnostic criteria and recognize the full spectrum of signs and symptoms of anaphylaxis
- appreciate the impact that various comorbidities and medications have on the response to treatment in patients with anaphylaxis
- describe the immediate and secondary management of a patient with anaphylaxis
- understand the need for further investigations and appropriate onward referral

Anaphylaxis

The first recorded episode of anaphylaxis can be found in hieroglyphic recordings from 2640 BC of the death of an Egyptian pharaoh after a wasp sting. A more modern description of anaphylaxis is described in a study from 1902 involving protocols for immunizing dogs with jellyfish toxin. The injection of small amounts of toxin in some animals, rather than generating protection, precipitated a rapid onset of fatal or near-fatal symptoms. The term 'anaphylaxis' is derived from the Greek roots 'ana' (backward) and 'phylaxis' (protection or immunity).

Definition and classification

The European Academy of Allergy and Clinical Immunology (EAACI) Nomenclature Committee proposed the following definition: Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction. Traditionally Anaphylaxis is a term used to describe immunoglobulin E (IgE)-dependent events and 'anaphylactoid reaction' is used to describe IgE-independent reactions — although both of these reactions are clinically indistinguishable.

The World Allergy Organization (WAO) has proposed that this nomenclature be discarded and that anaphylaxis should be described as immunologic and non-immunologic. The WAO is an international organization that represents many regional and international societies dedicated to allergy and clinical immunology.

- Immunologic anaphylaxis includes:
  - IgE-mediated reactions.
  - IgG-mediated reactions.
  - Immune complex/complement-mediated reactions.
- Non-immunologic anaphylaxis is caused by agents or events that induce sudden and massive mast cell or basophil degranulation in the absence of immunoglobulins.

Definitions and incidence

Uniphasic anaphylaxis is the most common type accounting for 80–90% of all episodes. The uniphasic response peaks within 30–60 minutes after exposure to allergens and tends to resolve either spontaneously or with treatment within the next 30–60 minutes.

Biphasic anaphylaxis has an estimated incidence of 1–23% of all anaphylactic reactions. These reactions are characterised by a uniphasic response, followed by an asymptomatic period of an hour or more and the subsequent recurrence of symptoms WITHOUT re-exposure to the antigen. These reactions can occur at any age.

Protracted anaphylaxis has an unknown incidence. These anaphylactic reactions last hours, days or even weeks in extreme cases without resolving completely.

Epidemiology

The incidence of anaphylaxis is underestimated in various studies in the UK owing to the problems of recognizing it. The criteria for inclusion vary in different studies and countries.

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Incidence

The American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group concluded that the overall frequency of episodes of anaphylaxis is between 30 and 950 cases per 100,000 persons per year.

Lifetime prevalence

The same group provided data indicating a lifetime prevalence of between 50 and 2000 episodes per 100,000 persons or 0.05–2%. More recent UK primary care data concur, indicating a lifetime age-standardized prevalence of a recorded diagnosis of anaphylaxis of 75.5 per 100.000 in 2005. Calculations based on these data indicate that approximately 1 in 1333 of the British population have experienced anaphylaxis at some point in their lives.

Pathophysiology

Immunologic reactions

IgE-mediated: this reaction is classically initiated by the antigen (allergen) interacting with the allergen-specific IgE bound to the receptor Fc on the mast cells and/or basophils. The B cells differentiate into IgE-producing cells via the activity of CD4-Helper T cells (Th2 cells). This occurs in the peripheral lymphoid tissues. The cytokines interleukin-4 and interleukin-13 along with their receptors contribute to the IgE response. Once produced, allergen-specific IgE diffuses into the tissues and vasculature and occupies the receptors on the mast cells and basophils. When the allergen diffuses into the proximity of a mast cell or basophil, it interacts with the surface bound IgE that is specific for that allergen. This interaction causes the receptors to initiate intracellular signalling. Certain allergens are able to interact on two or more surface receptors of IgE and thus are capable of cross-linking. If signalling is robust enough it will activate mast cells and basophils and cause degranulation. The result is the release of preformed mediators, enzymes and cytokines (tryptase, histamine and tumour necrosis factor) and the production of additional mediators, cytokines and enzymes. These mediators either act directly on tissue or indirectly by activating eosinophils to cause the symptoms of allergy.

IgG-mediated anaphylaxis has not been demonstrated in humans. However, human IgG receptors are capable of activating macrophages and neutrophils to secrete platelet activating factor (PAF) which activates mast cells causing **immune complex –complement mediated anaphylaxis**. This type of anaphylaxis has been implicated in life-threatening reactions to many drugs like protamine.

Non-immunologic reactions

The potential mechanisms by which mast cells and basophils are activated without the involvement of IgE or immune complexes are:

- Activation of complement in the absence of immune complex formation. This mechanism has been implicated in peanut-induced anaphylaxis, use of drugs dissolved in Cremophor EL including older preparations of propofol and paclitaxel.
- Direct activation of the mast cells and/or basophils. The exact mechanism is by activation of MRGPRB2 and MRGPRX2. This mechanism is implicated in the 'red man syndrome' reaction to vancomycin and degranulation by drugs such as opiates.
- Angiotensin-converting enzyme (ACE) inhibitors cause rare anaphylactic reactions or isolated angioedema due to the excessive production and/or accumulation of bradykinin.
- Over-sulphated chondroitin sulphate (OSCS) which is a compound contaminating heparin supplies in 2007–2008 caused direct activation of the kinin-kallikrein pathway which generated bradykinin, C3a and C5a.

Diagnostic criteria

The diagnostic criteria for anaphylaxis were published by a group of experts in 2005 and 2006 to aid clinicians in the recognition of the full spectrum of signs and symptoms.

Anaphylaxis is highly likely if **ONE** of the following criteria is fulfilled:

Criterion 1 – Acute onset (minutes to several hours) involving skin, mucosal tissue or both (generalized hives, urticaria, pruritus and flushing, swollen lips–tongue–uvula) **and at least one of the following**:

- Respiratory compromise (bronchospasm, wheeze, stridor, hypoxaemia, reduced peak expiratory flow).
- Reduced blood pressure (BP) or associated symptoms and signs of end-organ dysfunction (collapse, syncope, incontinence).

Criterion 2 – **Two or more of the following** that occur rapidly after exposure **to a likely allergen for that patient** (minutes to several hours):

- Involvement of skin and mucosal tissue as described above.
- Respiratory compromise as described above.
- Reduced BP or associated signs and symptoms of reduced BP.
- Persistent gastrointestinal signs and symptoms (crampy abdominal pain, nausea, vomiting).

Criterion 3 – Reduced BP after exposure **to a known allergen for that patient** (minutes to several hours):

- Reduced BP in adults is defined as a systolic BP (SBP) of less than 90 mmHg or 30% decrease in that patient's baseline.
- In infants and children, reduced BP is defined as low systolic BP (age specific) or greater than 30% decrease in SBP.

Symptoms and signs

Common symptoms and signs include the following:

- Skin-mucosal signs and symptoms, which occur in up to 90% of all episodes include generalized hives, pruritus, flushing swollen lips–tongue–uvula, periorbital oedema, conjunctival swelling.
- Respiratory symptoms and signs, which occur in up to 70% of episodes. These include nasal discharge, nasal congestion, change in voice, choking sensation, stridor, wheeze, cough and shortness of breath.

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