Special Article

Anaphylaxis

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Anaphylaxis must always be considered a medical emergency. While classic anaphylaxis needs specific antigen to trigger IgE antibody-mediated reaction, idiopathic anaphylaxis spontaneously occurs with no external allergen. Anaphylactoid are not mediated by antigen-antibody but result from substances acting directly on mast cells and basophils.

Incidence of anaphylaxis is 21 per 100,000 person-years with fatality in about 0.65% of cases. Food is the most frequent cause of anaphylaxis in children while insect sting is the most common cause in adults. Epinephrine is the first pharmacological treatment. Secondary measures include circulatory support, H1 and H2 antagonists, bronchodilators if necessary and probably corticosteroids. Since life-threatening manifestations may recur during the recurrent phase, it may be necessary to observe the patients for up to 48 hours after apparent recovery from an anaphylactic episode.

Keywords: *Anaphylaxis, Anaphylactoid, Idiopathic anaphylaxis, Allergic reaction, Uniphasic, Biphasic, Paotracted, Epinephrine*

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Anaphylaxis is defined as "a serious allergic reaction that is rapid in onset and may cause death[1]". It is the most severe form of allergy and must always be considered a medical emergency. Characteristically this systemic reaction occurs rapidly after exposure to an allergy-causing substance and resolves spontaneously within minutes to hours[2], probably because of the body's compensatory mechanisms[3].

Epidemiology

The actual rate of occurrence of anaphylaxis is difficult to determine as it is commonly undiagnosed and its definition varies considerably. Mild episodes, although potentially fatal, often are unrecognized[4]. Fatal reactions are likely to be under reported, e.g. insect stings induced anaphylaxis may be concluded as unexplained outdoor death while fatal food reaction can be misinterpreted as asthma death. Regardless of the problems in estimation, a careful epidemiologic study of the reported occurrences of anaphylaxis from all causes over a specific time period in a closed population found this reaction in 21 cases per 100,000 person-years with fatality in about 0.65% of cases[5]. Recent analysis from Thammasat University Hospital in Thailand found an occurrence rate of 223/100,000 patients per year[6]. The best insight into the incidence is perhaps obtained from assessing prescriptions for automatic epinephrine injectors, which identified an overall incidence of about 1% of the population of Manitoba, Canada[7]. The incidence of anaphylactic episodes seems to be increasing[8]. It usually occurs in a community rather than in a healthcare setting[5]; in persons of higher rather than lower socioeconomic status[9] and in adults rather than in children[10]. Under the age of 16, males experience anaphylaxis more frequently than females[7] while after puberty, females predominate[11]. Atopic history is more frequently established in patients experiencing IgE-mediated anaphylactic reactions to agents administered orally rather than parenterally and in patients who succumb to non-IgE-mediated anaphylactoid episodes.

Recurrent anaphylaxis, upon re-exposure to the same substance, is common but does not always happen. Depending on different kinds of triggering allergens, the risk for reaction to another exposure has been estimated to be 40-60% for insect stings[12], 20-

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40% for radiocontrast agents[13] and 10-20% for penicillin[14]. The severity of reaction to repeated exposure does not have to be the same as the initial event. If the antigen was administered continuously, the risk or severity of reaction might be decreased. Recurrent episode is also less likely to occur if a considerable length of time has elapsed since the last reaction.

Causes of anaphylaxis

Systemic anaphylaxis arises when mast cells are activated to secrete mediators that bring out a systemic response. Mediators released by mast cells include pre-formed histamine stored in secretory granules, newly synthesized products of arachidonic acid i.e. prostaglandins and leukotriene and an array of cytokines and chemokines[15]. These mediators cause bronchial and gastrointestinal smooth muscle contraction, vascular muscle relaxation and increased permeability of post capillary venules; and account for many signs and symptoms of anaphylaxis. Excessive levels of histamine in the CNS may explain the sense of doom commonly experienced at the onset of systemic anaphylaxis. Although many mechanisms, both immunologic and non-immunologic, can initiate mast cell secretions; they do not differ in their clinical presentation and are treated in the same manner[2].

I. Immunologic

1.1 IgE mediated anaphylaxis

Classic anaphylaxis occurs when there is cross-linking between the high affinity IgE receptors on the membranes of mast cells and basophils through antigen-antibody interaction. This leads to rapid degranulation release of histamine, followed by synthesis and release of leukotrienes, prostaglandins, cytokines, and other mediators of the allergic response.

Potential allergens that trigger anaphylactic reaction via this mechanism include:

Food: Peanut, tree nut, shellfish, finfish, milk and egg are most frequently implicated in anaphylaxis especially in children[16,17]. Although unusual, bird's nest soup, which is one of the popular health foods in Thailand, has also been reported as the inciting allergens of anaphylaxis from the Asia-Pacific region[18].

Cross-reactivity between pollen and food exists, such as with ragweed pollens and the melons, cucumbers and banana[19], or grass pollens and apples, oranges, cherries and tomatoes[20].

A subset of patients has anaphylaxis if exercise is performed within 2 to 6 hours of food ingestion[21]. These patients will, however, tolerate either food or exercise independently. Thus, anaphylaxis can be prevented with avoidance of food ingestion 4 to 6 hours prior to or following exercise[22].

Antibiotics: Penicillin has been surpassed by foods as the most common cause of anaphylaxis[16].

Serious reactions to penicillin occur about twice as frequently following parenteral versus oral administration. Cross-reactivity exists between penicillin and the various b-lactam antibiotics, including imipenem and meropenem.

Compared with the first and second generation cephalosporins, the third generation cephalosporins has a lower incidence of clinically relevant cross-reactivity with penicillin (16%, 10% and 2-3% respectively)[23-25].

Although atopic background does not predispose an individual to the development of penicillin hypersensitivity, once sensitized, such individuals are at increased risk for severe or fatal anaphylaxis[14]. Mold sensitivity is not a risk factor for penicillin allergy. Muscle relaxants account for 50-75% of all allergic reactions occurring during general anesthesia. Antibiotics, other anesthetic agents and latex are the other causes of intra-operative anaphylaxis. Reaction typically occurs following previous sensitization to the drug or related agent. Risk factor is the female sex.

Insect venoms: Systemic reaction to insect stings occurs in about 3.3% of the population and is the most common cause of anaphylaxis in adults[26]. The most common species are the Hymenoptera (bee, wasp, yellow-jacket, hornet, fire ant). Their venoms contain phospholipases, hyaluronidases and other enzymes that can elicit an IgE response. Reactions to Hymenoptera stings occur more frequently in males than in females.

Latex: Anaphylactic reactions are mediated by IgE antibody to rubber tree proteins left in latex gloves, condoms and medical devices[27]. Exposures can be topical, airway, mucosa, surgery, catheterization and dental procedures. Individuals at greater risk are health care workers, rubber industry workers and children with spina bifida or severe urogenital defects[27].

Foreign proteins including insulin, seminal proteins, heterologous antiserum against snake-venom, blood components, streptokinase, chymopapain, vaccines and allergen immunotherapy can also cause anaphylaxis.

1.2 IgE independent anaphylaxis

Immunologic reactions can induce anaphylaxis via complement activated immune complexes (type

II) such as intravenous immunoglobulin and possibly dextran. Cytotoxic reactions (type III) as that occurring in a mismatched blood transfusion reaction can also activate complement-causing perturbation of mast cells, resulting in anaphylaxis.

II. Non-immunologic (Anaphylactoid or pseudo-allergic reactions)

Degranulation of mast cells can also occur via:

2.1 Activation of the complement and coagulation systems by hyperosmolar iodinated contrast media, dialysis membranes and possibly protamine can lead to degranulation of mast cells causing anaphylaxis.

2.2 Narcotics directly activate mast cell degranulation causing elevated plasma histamine levels and non-allergic anaphylaxis.

2.3 Modulators of arachidonic acid metabolism such as aspirin and other conventional nonsteroidal anti-inflammatory drugs (NSAIDs) can cause anaphylactoid reactions[28]. Such patients characteristically react to only one NSAID or to aspirin. Cross-reactivity within the entire class of cyclooxygenase inhibitors is rare. Although some such reactions occur after two or more exposure to the same NSAID, specific IgE has not been found. COX-2-selective inhibitors are relatively safe in aspirin-sensitive asthmatics, but have not been adequately tested in aspirin-sensitive anaphylaxis subjects.

III. Idiopathic causes

Flushing, tachycardia, angioedema, urticaria, upper airway obstruction and other signs and symptoms of anaphylaxis can occur without a recognizable cause. The diagnosis is confirmed in doubtful cases by the elevated plasma concentration of the mast cell enzyme, tryptase, which is specific for mast cell degranulation. Serum tryptase levels peak 1-1.5 hours after onset of anaphylaxis and remain elevated for five hours, but are stable while refrigerated, and may be assayed in serum previously obtained for other purposes[29]. Measurement of urinary histamine levels can also be helpful as they are able to remain elevated for longer periods than the plasma histamine[29,30].

Diagnosis

In anaphylaxis, multi-system involvement is normal. The most common symptoms are urticaria and angioedema, followed by upper airway edema, wheeze, flush, hypotension, gastrointestinal symptoms and rhinitis respectively[10]. The onset and course of anaphylaxis may vary considerably from patient to patient. Initial symptoms may develop rapidly within minutes or may be delayed for up to 2 hours after exposure to the triggering agents. Usually, the more rapid the onset, the more severe is the reaction. The course of anaphylaxis can be uniphasic, biphasic or protracted. In biphasic pattern, signs and symptoms may clear either spontaneously or with treatment only to reappear within 8 hours of quiescent period[31]. Protracted anaphylaxis can begin as uniphasic or biphasic, with persistent symptoms despite therapy, and often lasting for days or weeks.

Severity of anaphylactic reaction can be graded as[32]

1. Mild reactions involve only the cutaneous system which usually manifest as erythema, urticaria and angioedema

2. Moderate reactions will involve gastrointestinal system, respiratory system or cardiovascular system. Clinical manifestations include dyspnea, stridor, wheeze, nausea and vomiting, abdominal pain, dizziness, diaphoresis, and chest or throat tightness.

3. Severe reactions will manifest with hypoxia and hypotension. Clinical symptoms are cyanosis, collapse and incontinence.

Predictors of severity are old age, insect venoms, iatrogenic causes and pre-existing lung diseases.

The diagnosis of anaphylaxis is usually readily apparent from rapid profound combinations of hypotension, tachycardia, urticaria, bronchospasm, angioedema, colics and diarrhea; often associated with sense of doom; and beginning within minutes of the provoking stimulus. When sudden collapse occurs in the absence of urticaria, generalized erythema or angioedema, other diagnoses including myocardial infarction, cardiac arrhythmia, septic shock, hemorrhagic shock, pulmonary embolism, insulin reaction, vasovagal reaction, hyperventilation and even globus hystericus must be considered. The most common is vasovagal collapse. In this situation, pallor and diaphoresis are common features associated with presyncopal nausea while pruritus or cyanosis is absent. Respiratory distress does not occur and the pulse is slow. Symptoms are immediately reversed by recumbence and leg elevation. In the presence of laryngeal edema and abdominal pain, hereditary angioedema must be considered. This disorder usually lacks pruritic urticaria and hypotension, has a slower onset and longer duration of attack and a family history of similar

reactions is often established. Patients with "Restaurant syndromes" from monosodium glutamate (MSG) may mimic anaphylaxis by presenting with flush reactions, chest pain, headache, diaphoresis, nausea and vomiting. History of previous attack within 1 hour after eating Chinese food is usually elicited.

Other disorders in the differential diagnosis include carcinoid syndrome, in which urticaria and profound hypotension are not typically associated; pheochromocytoma, which causes episodic hypertension; panic attacks and vocal cord dysfunction, which can be distinguished from anaphylaxis by history alone and other factitious allergic diseases[33].

Measurement of serum tryptase levels within several hours after an event is helpful in the differential diagnosis. Skin testing or in vitro measurements of antigen-specific IgE should be delayed for at least two weeks after the attack to prevent false negative results.

Treatment

Immediate therapy of systemic anaphylaxis requires that airway patency, blood pressure and cardiac status be assessed. Rapid treatment with epinephrine is of utmost importance. It has been shown that delays in administration have been associated with biphasic anaphylaxis and worse outcomes[31]. Intramuscular injection is recommended since it results in prompt elevation of plasma concentration[34]. Intramuscular injection of the 1-inch needle is preferable[35]. Delayed absorption was observed if epinephrine was injected subcutaneously. Intravenous epinephrine should be used only in a terminal patient.

The recommended dosage for controlling symptoms and maintaining blood pressure is 0.01 mg/kg (maximum 0.5 mg) of aqueous epinephrine administered intramuscularly every 5 to 15 minutes as necessary[36].

Causes of epinephrine failure include:

o Rapid progression of reaction

o Failure to inject epinephrine promptly, adequately, and properly

o Patients taking a beta-blocker medication

Glucagons may be used in patients taking a β-blocker. Parenteral injection of H1 and H2 anti-histamines may prevent progression of some signs and symptoms.

Glucocorticoids do not reliably prevent biphasic anaphylactic event and are unlikely to be of benefit acutely. Patients who have experienced an anaphylactic reaction are at greatest risk to suffer another episode. A reasonable length of time for observing the post-anaphylactic patient is 4 to 6 hours, with prolonged hospital admission up to 48 hours for patients with severe or refractory symptoms[1]. All patients discharged should receive information about how to avoid the precipitating allergen (if known) and have education for self-injectable epinephrine. β-blockers and ACE inhibitors as well as agents to which they are sensitive should be avoided. Immunotherapy for venom-sensitive subjects, desensitization for certain cases of drug allergy, and anti-IgE therapy for subjects at risk of food induced anaphylaxis should be considered. False assumptions in anaphylaxis always result in worse outcome and usually include:

- Anaphylaxis is always preceded by mild symptoms.

- There is no need to rush because there is always time to get to a hospital.

- Epinephrine is always effective.

- A mild reaction will not progress and will go away.

- Antihistamines are effective by themselves in the treatment of anaphylaxis.

In conclusion, key features in the management of acute anaphylaxis are rapid and aggressive administration with intramuscular epinephrine, even in patients with a cardiac history, along with maintenance of adequate intravascular volume with early and aggressive administration of intravenous fluids together with 100% oxygen delivery.

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ภาวะช็อกจากโรคภูมิแพ้

สุชีลา จันทรวิทยานุชิต

ภาวะช็อกจากโรคภูมิแพ้เป็นปฏิกิริยาตอบสนองต่อสิ่งแปลกปลอมที่รุนแรงที่สุดของระบบภูมิคุ้มกัน แม้ว่าปัจจุบันจะพบได้ไม่บ่อย แต่ก็เป็นภาวะช็อกที่รักษาง่ายที่สุดถ้าสามารถวินิจฉัยได้ถูกต้องและแก้ไขได้ทันท่วงที กลไกการเกิดภาวะนี้อาจเป็นได้ทั้งจากปฏิกิริยาที่อาศัย IgE เป็นสื่อกลาง โดยแอนติเจนเข้าไปจับกับ IgE ที่เกาะอยู่บน mast cells ทำให้เกิดการหลั่งสารตัวกลางออกมากระตุ้นให้เกิดอาการของอวัยวะต่าง ๆ ทั่วร่างกายที่เรียกว่า systemic anaphylaxis หรืออาจเกิดจากสารแปลกปลอมเข้าไปกระตุ้น mast cell หรือ complement cascade โดยตรง ไม่ต้องผ่าน IgE ทำให้เกิด pseudoallergic reaction ที่เรียกว่า anaphylactoid ก็ได้ อุบัติการณ์ของการเกิดภาวะช็อกจากภูมิแพ้ พบได้ประมาณ 21รายต่อประชากร 100,000 รายต่อปี โดยมีอัตราตายประมาณ 0.65%ของผู้ป่วย การแพ้อาหารเป็นสาเหตุที่พบบ่อยที่สุดในเด็ก ในขณะที่ผู้ใหญ่มักเป็นจากพิษแมลงต่อย สำหรับการรักษา ยาที่ต้องให้ผู้ป่วยเป็นตัวแรกคือ epinephrine ถัดจากนี้ก็ได้แก่ circulatory support, H1 และ H2 antagonists, bronchodilators และ corticosteroids ถ้าจำเป็น และเนื่องจากผู้ป่วยอาจมีอาการเป็นซ้ำได้อีก จึงควรรับผู้ป่วยไว้สังเกตอาการต่ออีก 48 ชั่วโมงหลังจากที่ดีขึ้นแล้ว