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REVIEW

An overview of anaphylaxis in children

Nevin CAMBAZ KURT

Department of Pediatry, Başakşehir Çam and Sakura City Hospital, İstanbul, Turkey

ORCID ID
NCK : 0000-0003-4066-1834

ABSTRACT

Anaphylaxis is an acute and life-threatening systemic hypersensitivity reaction. Anaphylaxis is an immunoglobulin E-mediated reaction, Food allergy is the most common cause of anaphylaxis, followed by drugs. Patients with anaphylaxis commonly present with symptoms involving skin or mucous membranes, followed by respiratory and gastrointestinal symptoms. Epinephrine is the drug of choice for treating anaphylaxis. Patients and caregivers should be educated on the use of epinephrine autoinjectors and symptoms of anaphylaxis.

Keywords: Allergy, anaphylaxis, children.

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Correspondence: Nevin CAMBAZ KURT, MD. Başakşehir Çam ve Sakura Şehir Hastanesi, Pediatri Kliniği, İstanbul, Turkey.
Tel: +90 212 909 60 00 **e-mail:** nevinbinnurkurt@gmail.com

DEFINITION

Anaphylaxis is an acute-onset, life-threatening, systemic hypersensitivity reaction with a wide spectrum of clinical symptoms. Immediate release of mediators from mast cells and basophils is the underlying mechanism in anaphylaxis.[1] Anaphylaxis is a potentially fatal condition that requires prompt diagnosis and timely and effective treatment. Every physician should have sufficient knowledge about the symptoms and treatment of anaphylaxis.

Anaphylaxis was first used as a term by Richet and Portier in 1902 during vaccination studies in dogs and was defined as symptoms that occur against immunity. The first case of anaphylaxis in history is the death of Egyptian pharaoh Menes as a result of a bee sting in 2640 B.C.[2]

According to the new terminology, anaphylaxis caused by immunological pathways such as immunoglobulin (Ig)E, IgG, and complement system is defined as allergic (immunological) anaphylaxis. Anaphylaxis caused by non-immunological mechanisms, which was previously defined as anaphylactoid reaction, is defined as non-allergic anaphylaxis. Anaphylaxis that occurs without encountering any substance is defined as idiopathic anaphylaxis.

ETIOLOGY - EPIDEMIOLOGY

Although the exact frequency of anaphylaxis is unknown, lifetime prevalence is estimated to be between 0.05% and 2%.[3] Anaphylaxis is more common in children. In a study by Decker et al.,[4] the incidence of anaphylaxis was reported as 49.8/100,000 people/year for all ages and 70/100,000 people/year for 0–19 years. The incidence of anaphylaxis has been observed to be increased recently, especially in young people.[5] It is also noteworthy that there is an increase in the rate of food-induced anaphylaxis-related hospitalization among children.[6] The increase in hospitalizations is especially common in children aged 10 years and younger. Lin et al.[7] found a 4-fold increase in the rate of hospitalization in this age group between 1990 and 2006.

The most common causes of anaphylaxis in all age groups are food, drug, and insect bites. The most common foods causing anaphylaxis are cow's milk, eggs, soy, peanuts, hazelnuts, fish, and shellfish. Antibiotics and nonsteroidal anti-inflammatories are the most common cause of drug-induced anaphylaxis. Latex, aeroallergens, and vaccines are other rare causes of anaphylaxis. Among children, food is the most common cause of anaphylaxis followed by drugs.[8] In a retrospective study conducted in our country, food was found to be the cause of anaphylaxis in 38.4%, followed by venom (37.5%) and drugs (21%).[9]

PATHOPHYSIOLOGY

Anaphylaxis classically occurs through the release of mediators as a result of the degranulation of mast cells and basophils via IgE. These mediators can be divided into two groups: (i) pre-synthesized mediators such as histamine, heparin, tryptase, chymase, carboxypeptidase A3, tumor necrosis factor a (TNF-a), cathepsin G; (ii) newly synthesized mediators such as platelet-activating factor (PAF), prostaglandin (PG) D2, leukotriene (LT) C4, cytokines interleukin (IL) -5, IL-6, IL-8, IL-13, IL-33, TNF-a and granulocyte macrophage colony-stimulating factor and chemokines (MIP-1a, MIP-1b ve MCP1). Rarely, mast cells and basophils can be immunologically stimulated without the mediation of IgE.[10]

Anaphylaxis can also develop by non-immunological mechanisms. Physical factors such as exercise, cold, heat, sunlight/UV radiation, drugs such as ethanol and opiates cause anaphylaxis by direct degranulation of mast cells.[10]

Mediator release from mast cells can occur without any cause. This condition is defined as idiopathic anaphylaxis and diagnosed in cases with no identified cause for anaphylaxis. The exact prevalence of idiopathic anaphylaxis is unknown. The clinical manifestations of idiopathic anaphylaxis are similar to general signs of anaphylaxis, including typical acute onset and worsening of signs in minutes or hours. The pathophysiology has not yet been fully elucidated, but an IgE-mediated pathway by yet unidentified triggers is suggested to be the main underlying mechanism in idiopathic anaphylaxis.[11]

SIGNS AND SYMPTOMS

Anaphylaxis is a multisystem organ reaction which most frequently includes skin, mucous membranes, respiratory, cardiovascular, gastrointestinal, and neurological systems. Clinical symptoms often occur within 5–30 min following parenteral administration of the culprit antigen, and may sometimes occur within 1 h or more. Symptoms usually occur within the first 2 h after oral ingestion or may delay up to several hours. The faster the reaction occurs, the greater the severity of anaphylaxis. The risk of death is higher in early-onset reactions. Initial symptoms include boredom, fear of death, dizziness, and fainting.[12]

At the onset of an anaphylactic reaction, "prodromal symptoms," manifested by mild itching, burning sensation on the palms and soles or anogenital region, metallic taste, anxiety, headache, and disorientation, can be observed.[3] Although cutaneous symptoms are observed in 80–90% of cases, anaphylaxis can develop without skin involvement, which makes it difficult to diagnose.[13] Respiratory symptoms are more common in children while cardiovascular system symptoms are more prominent in adults.[14]

The reappearance of anaphylactic symptoms without re-exposure to the responsible allergen after complete resolution of anaphylaxis is defined as a biphasic reaction and is usually seen within the first 12–72 h after the initial reaction has resolved.[15]

The clinical findings of anaphylaxis by systems are summarized in Table 1.

DIAGNOSIS

The diagnosis of anaphylaxis is mainly based on clinical findings. A detailed history should be taken quickly. However, history taking should not cause a delay in treatment. Particularly, timing of trigger exposure and beginning of symptoms, and presence of any other disease as a possible cause of current symptoms should be clarified in patient history. Possible triggers include food, medicine, insect bites, exercise, exposure to hot or cold, in the past 6 h be-

Table 1: The clinical findings of anaphylaxis by systems

Skin-mucosa (80–90%)
Urticaria, angioedema, morbilliform rash
Itching, tingling, hot flashes, flushing
Periorbital pruritus, swelling, erythema, conjunctival pruritus, discharge
Itching and swelling of the lips, tongue, uvula, and soft palate
Itching in the external ear canal, palms, soles, and genital area
Respiratory system (40–70%)
Nose: Discharge, congestion, itching, sneezing
Larynx: Hoarseness, choking sensation, stridor, dysphonia, dysphagia,
Lung: Shortness of breath, wheezing, bronchospasm, respiratory failure, cough, chest tightness
Cyanosis
Cardiovascular (10–45%)
Hypotension
Tachycardia, bradycardia, dysrhythmia
Chest pain, palpitations
Shock, syncope
Arrhythmia
Cardiac arrest
Gastrointestinal (30–45%)
Nausea-vomiting
Abdominal pain-cramp
Diarrhea
Neurological (10–15%)
Fear of death, restlessness
Consciousness changes, convulsions
Confusion
Headache, blurred vision
Sudden behavioral changes
Restlessness (sudden behavior change in infants and young children, for example, irritability, quitting play)
Other
Sweating, incontinence
Metallic taste in the mouth, dysphagia
Uterine contractions

fore the anaphylaxis attack. For female patients, information about the menstrual cycle is also important.[16] In addition, the duration of symptoms and medications given for treatment need to be obtained.

In 2006, the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network proposed criteria for diagnosis of anaphylaxis (Table 2).[17]

LABORATORY STUDİES

The diagnosis of anaphylaxis is usually based on clinical symptoms. However, laboratory tests such as serum tryptase and histamine levels can be used in some patients. Serum histamine level measured between 15 min and 1 h after the onset of symptoms may help the diagnosis.[1] High serum tryptase level (>11.4 mcg/L) obtained between 15 min and 3 h after symptom onset supports the diagnosis of anaphylaxis.[12] However, normal serum tryptase levels do not exclude the diagnosis.[2] Markers showing mast cell activation such as carboxypeptidase A3, chymase, PAF, cytokines (LT-E4 and 9-a, 11-b PG-F2 in urine) are also used in the diagnosis of anaphylaxis. Today, basophil activation test can also be used in the diagnosis of anaphylaxis.[2]

DIFFERENTIAL DIAGNOSIS

The most common clinical condition similar to anaphylaxis is vasovagal syncope. However, in anaphylaxis, tachycardia usually occurs while acute hypotension and bradycardia develop as a result of vagal stimulation in vasovagal syncope. Other symptoms of vasovagal syncope include pallor and sweating. There are no cutaneous signs such as urticaria, or respiratory symptoms in vasovagal syncope attack.

Asthma attack, urticaria, panic attack, hyperventilation syndrome, and shock are the other conditions included in the differential diagnosis of anaphylaxis.[12]

TREATMENT

Early diagnosis and prompt treatment are essential in the management of anaphylaxis and often determine the prognosis. Adrenaline is the first drug to be given and should not be delayed. There is no absolute contraindication for the administration of adrenaline.[2] Even in the elderly and people with cardiovascular disease, the benefit of adrenaline outweighs the risks.[1] Adrenaline should be administered intramuscularly (IM) to the anterior-lateral thigh (vastus lateralis muscle) with dose of 0.01 mg/kg (0.01 ml/kg). The maximum dose of adrenaline is 0.3 mg in children and 0.5 mg in adults. Repeat adrenaline doses can be given every 5–10 min when necessary. In case of refractory anaphylaxis, adrenaline infusion should be started.[18] When an adrenaline auto-injector (AAI) is used, 0.15 mg/dose is administered to children weighing 7–25 kg, and 0.3 mg/dose to children over 25 kg.[19]

Second-line treatment of anaphylaxis includes removing the triggering factors, positioning the patient appropriately, maintaining oxygen and fluid support, and administration of inhaled beta-2 agonist therapy. However, these treatments are supportive treatment, not life-saving, therefore should be applied after adrenaline.[20] Stabilization of vital signs and maintaining airway patency and adequate circulation are critical. These patients should be laid down with raised feet to provide venous return to the heart. Patients with hypotension should be kept in a lying position until they are asymptomatic. Deaths have been reported in patients who stand up in the early period.[3] High-flow oxygen (6–8 L/min)[2] is used for respiratory support. If hypotension persists despite adrenaline therapy, IV crystalloid (saline) or colloidal fluid support, 20 ml/kg in the 1st h for children, should be

Table 2: National institute of allergy and infectious disease and food allergy and anaphylaxis network criteria for anaphylaxis

Anaphylaxis is likely when any one of these three criteria is fulfilled

1. Acute onset of illness (within minutes or hours) with involvement of the skin, mucous membranes, or both (common urticaria, itching or flushing, swelling of the lip, tongue-uvula) and at least one of the following:
   a) Respiratory problem (dyspnea, wheezing, bronchospasm, stridor, decrease in peak expiratory flow-peak expiratory flow, hypoxemia)
   b) Hypotension or related symptoms of end-organ dysfunction (hypotonia, collapse, syncope, and incontinence)
2. Two or more of the following that develops minutes or hours after exposure to a possible allergen:
   a) Hypotension or associated symptoms (hypotonia, collapse, syncope, and incontinence)
   b) Respiratory distress (dyspnea, wheezing, bronchospasm, stridor, decrease in PEF, and hypoxemia)
   c) Persistent gastrointestinal symptoms (cramping abdominal pain, vomiting)
   d) Skin and/or mucosal involvement (common urticaria, pruritus-flushing, swelling of tongue-lip-uvula)
3. The development of hypotension within minutes or hours of the patient's exposure to a previously known allergen:
   a) For infants and children: Low systolic blood pressure for age or more than 30% decrease in systolic blood pressure
   b) For adults: A systolic blood pressure of <90 mmHg or a decrease of more than 30% from the person's baseline systolic blood pressure.

Limits of hypotension: <70 mmHg between 1 month and 1 year, 70 + ([2 × age]) mmHg between 1 and 10 years, and <90 mmHg between 11 and 17 years.

given.[21] If there is no vascular access, intraosseous route is used for fluid support. For bronchospasm, inhaled salbutamol (0.15 mg/kg) for 15–20 min is used with a maximum of 6 doses.[12] In patients who develop stridor due to laryngeal edema, nebulized adrenaline (2–5 mL, 1 mg/mL) is used in addition to IM adrenaline.[18]

Third-line therapy of anaphylaxis includes H1 and H2 antihistamines and glucocorticoids. Antihistamines are often used in the treatment of anaphylaxis; however, they are only recommended for reducing skin symptoms.[20] Corticosteroids are used in the treatment of anaphylaxis to prevent prolonged anaphylaxis symptoms. Methylprednisolone 1–2 mg/kg per dose is given intravenously every 6 h (maximum 50 mg). There is no definite evidence that corticosteroids prevent biphasic reactions.[22]

The drugs and doses used in anaphylaxis were summarized in Table 3.

Table 3: Drugs and doses used in anaphylaxis

Drug	Dose	Maximum dose	Administration route
Adrenalin (1 mg/ml)	0.01 mg/kg	0.3 mg	Intramuscular
Diphenhydramine	1 mg/kg	50 mg	Intravenous
Ranitidine	1 mg/kg	50 mg	Intravenous
Methylprednisolone	1–2 mg/kg	50 mg	Intravenous
Salbutamol	2.5 mg	50 mg	Inhalation

MONITORING AND FOLLOW-UP

Since biphasic reactions in anaphylaxis mostly occur 4–6 h after the first symptoms, patients should be monitored at least 4–6 h.[23] Patients with respiratory symptoms are closely monitored for at least 6–8 h, and those with hypotension for at least 12–24 h.

A risk assessment should be made before discharge, an emergency action plan should be given in writing to the patient and the caregiver. AAI is prescribed for the following conditions:

1. All patients with a history of anaphylaxis
2. Patients with a previous history of systemic allergic reaction
3. Patients with food allergy and asthma
4. Patients with known allergies to peanuts, fish, and shellfish

Patients with IgE-mediated early-type food allergies also need to be evaluated for AAI prescription.[21] Patient and caregiver should be informed and trained about how and in which situations to use AAI. In Our country, AAI is produced under the name of Penepin. For follow-up, the patient should be referred to an allergy specialist to identify possible triggering factors and to provide precautions.

In summary, it is critical to be well-informed about anaphylaxis in advance as it is unpredictable and can result in death if treatment is delayed. Education of healthcare professionals about the symptoms, emergency treatment, and prevention of anaphylaxis is essential in the management of anaphylaxis. Training of patients and caregivers on when and how to use the AAI is an important point in the emergency treatment of anaphylaxis. Patient with a history of anaphylaxis should be directed to an allergy specialist.

Statement

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Peer-review: Externally peer-reviewed.

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