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In The Light of the Guidelines: Anaphylaxis

Klavuzlar Işığında Anafilaksi

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Öz

Anafilaksi, mast hücre mediyatörlerinin sistemik dolaşıma aniden salınmasına bağlı gelişen, yaşamı tehdit edebilen multisistemik bir hastalıktır. Çoğunlukla gıdalarla, ilaçlarla ve böcek sokmalarına karşı immunoglobulin E (IgE) aracılı reaksiyonlardan kaynaklanır ancak mast hücrelerinin degranülasyonuna neden olan bir ajanda neden olabilir. Eşlik eden ağır ve kontrolsüz astım, mastositozis, kardiyovasküler hastalıklar, bazal serum triptaz yüksekliği, beta bloker veya ACE inhibitör kullanımı, egzersiz, akut enfeksiyonlar ve duygusal stres anafilaksi riskini artıran nedenlerden birkaçıdır. Anafilaksi sırasında kalp ve solunum durması dakikalar içinde gelişebileceği için tanı konulduktan hemen sonra hızla tedavi edilmelidir. Tedavide verilmesi gereken en önemli ve ilk ilaç adrenalindir. Bu derlemede anafilaksinin tanı ve tedavisi güncel literatüre göre özetlenmiştir.

Anahtar Kelimeler: Anafilaksi, adrenalin, patofizyoloji, ayırıcı tanı, glukagon

Abstract

Anaphylaxis is a multi-systemic disease, which develops associated with the sudden expression of mast cell mediators into the systemic circulation, and can be life-threatening. The majority of cases are reactions to food, drugs, or insect stings, mediated by immunoglobulin E (IgE), and may cause a process resulting in degranulation of mast cells. Severe asthma, mastocytosis, cardiovascular disease, elevated basal serum triptase, the use of beta blockers or ACE inhibitors, exercise, acute infections and emotional stress are some of the reasons increasing the risk of anaphylaxis. As cardiac functions and respiration can halt within minutes during an anaphylaxis attack, treatment must be applied rapidly immediately after diagnosis. Adrenalin is the first and most important drug which should be given in treatment. In this review, the diagnosis and treatment of anaphylaxis are summarised in the light of current literature.

Key words: Anaphylaxis, adrenaline, pathophysiology, differential diagnosis, glucagon

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INTRODUCTION

Anaphylaxis is a potentially life-threatening, multisystemic disease which can develop as a result of the effect of mediators expressed from mast cells and basophils (1). That all healthcare personnel, and especially physicians in the Emergency Department, do not miss anaphylaxis and know that treatment must be applied early is life-saving. When one of the two accepted criteria for the diagnosis of anaphylaxis is fulfilled (Table 1), diagnosis is made with the help of the history and physical examination (2). When taking the history, questions must be asked to ascertain when and how the event happened, how long it lasted, whether any treatment was given, and triggers should be questioned in detail. Although anaphylaxis generally emerges within the first 2 hours, to avoid missing late cases, even though they are uncommon, questions must be asked about the period 4-6 hours before the event to determine drug and food intake, whether or not any bee or other insect sting was experienced, exercise status before the event, and exposure to heat and cold. Females in anaphylaxis should also be questioned about the association with the menstrual cycle (3).

Although diagnosis of anaphylaxis generally requires involvement of at least 2 organ systems, in some cases involvement of only one organ (hypotension) may be sufficient for diagnosis (2). The majority of anaphylaxis symptoms emerge within 2 hours of contact with the allergen. In food allergies, this period is 30 mins, and there may be more rapid onset in cases of parenteral drug use or insect stings (4, 5). Skin lesions are the most frequently seen anaphylaxis symptoms but in some cases they may not be seen at all or may not be determined at onset (6). Symptoms related to the respiratory system are observed more frequently in paediatric patients and symptoms related to the cardiovascular system in adults. To avoid missing mild anaphylaxis which can be observed, it is important to prevent not only the anaphylaxis at that moment but also any anaphylaxis attacks which could recur in the future (3). One of the most important reasons that a diagnosis of anaphylaxis is missed, is that the skin and mucosa symptoms do not always accompany the table. In these situations, other systemic findings of the patient must be examined in detail (6, 7). A biphasic reaction is when the reaction recurs up to 72 hours (mean 6-8 hours) after the recovery of symptoms during the course of anaphylaxis. A biphasic reaction may be seen to be more severe than the previous reaction. A delay in the administration of adrenalin, an insufficient dose, or not administering glucocorticosteroids can increase the risk of biphasic reaction (8).

Stimuli causing anaphylaxis

Several agents may cause anaphylaxis, such as foodstuffs, venom, latex, drugs, allergen immunotherapy, radiocontrast media, exercise, hormones, animal or human proteins, enzymes, and colourants. The most frequently determined agents are drugs, venom, and foodstuffs. However, no cause can be determined in 20% of cases (idiopathic anaphylaxis) (9). In a retrospective study in Turkey, the most common cause of anaphylaxis was reported to be drugs, followed by venom, then foodstuffs, latex, and exercise, respectively (7). Despite the development of anaphylaxis from any drugs, it is seen most often with antibiotics, and of these the beta-lactam group of antibiotics most frequently cause an anaphylactic reaction. Other currently used drugs causing anaphylaxis include non-steroidal anti-inflammatory drugs (NSAID), chemotherapy drugs (carboplatin, doxorubicin, asparaginases), and biological agents (cetuximab, rituximab, infliximab, and occasionally monoclonal antibodies such as omalizumab) (3). Of the agents used in imaging processes, radiocontrast media are known to have the highest risk of anaphylaxis (10). Latex, which is used in all the areas of daily life of healthcare workers is also a significant cause of anaphylaxis (11).

To be able to make a diagnosis of idiopathic anaphylaxis, other causes must be discounted. For this, a detailed anamnesis, skin tests for allergens which can be determined or may be occult, and serum specific IgE measurements are necessary. While idiopathic anaphylaxis is diagnosed by discounting other reasons, a diagnosis may be made of other conditions such as mastocytosis and clonal mast cell diseases, just as unexpected stimuli may be determined such as galactose alpha 1, 3 galactose (alpha-gal), which is found in red meat (3).

The Epidemiology of Anaphylaxis

In the last two decades there has been an increase in patient presentations associated with anaphylaxis, including infants. In the American Anaphylaxis Epidemiology Working Group report, prepared in 2006, lifetime prevalence was estimated to be 0.3%. In the light of data in the last 5 years, clearer numbers have been reached and the incidence has been reported to be 50-112 episodes/100,000 person-years and lifetime prevalence ranging between 0.3% and 5.1% (12, 13). The numbers are

higher in children, especially in the 0-4 years age group. Reports from various geographic regions, based on clinical and administrative data related to hospitalised patients, have shown an increase in the frequency of presentations (5-7-fold in the last 10-15 years). According to the data from voluntary death notifications by physicians and large national databases, death from anaphylaxis is frequently seen, at the rate of 0.35-1.06 per million people per year, without the increase seen in the last 10-15 years (13).

Risk Factors for Severe Anaphylaxis

Some of the reasons increasing the risk of anaphylaxis are severe and uncontrolled asthma, mastocytosis, cardiovascular disease, elevated basal serum triptase, the use of beta blockers or ACE inhibitors, exercise, acute infections, and emotional stress (14). Of the several demographic factors determined, advanced age has been observed to increase the risk of severe reaction (15-17). Moreover, the risk of drug-related fatal anaphylaxis has been determined to be greater in those of African-American race (15). Banerji et al (18) showed that females constituted 71% of 716 patients presenting at the Emergency Department and this finding was interpreted as possibly related to the drug sensitivity of female hormones and the severity of the allergic reaction. However, in another study, no such relationship was determined (15).

The method of drug administration is one of the reasons which changes the risk of anaphylaxis. Intravenous administration increases the risk of drug-related anaphylaxis and causes the reaction to be more severe (15-17).

The Pathophysiology of Anaphylaxis

The World Allergy Organization separates the mechanisms of anaphylaxis as immunological and non-immunological (2).

- Immunological Mechanisms:
- IgE-mediated reactions,
- Immunoglobulin G (IgG) – mediated reactions (not identified in humans)
- Complement-mediated reactions
- Non-immunological Mechanisms:
- Agents inducing sudden and massive mast cell or basophil degranulation in the immunoglobulin pathway

The majority of cases of anaphylaxis occurring with foodstuffs, venom, and drugs, are IgE-mediated reactions. IgE-mediated anaphylaxis occurs as a result of the allergen cross-linking to one or more IgEs bound to high-affinity IgE receptors (FcεRI) in the mast cells and basophils of the host. After this linking, clinical signs emerge through mediators and cytokines expressed by the cells. The pathophysiological event in which IgE- mediated anaphylaxis plays a role occurs in two phases. The first phase is sensitisation, and the second phase is mast cell or basophil degranulation when the allergen is encountered again (20). Non-immunological causes of anaphylaxis include exposure to cold, exercise, radiocontrast media, and various drugs (vancomycin, opiates, cyclogenase (COX-1 inhibitors). It has not been clarified by which mechanism mast cells are

Table 1. Anaphylaxis Diagnosis Criteria

Anaphylaxis is highly likely when any one of the following 2 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
a.Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
b.Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia, collapse, syncope, incontinence)
c. Severe gastrointestinal symptoms (eg, severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens
2. Acute onset of hypotensiona or bronchospasmb or laryngeal involvementc after exposure to a known or highly probable allergend for that patient (minutes to several hours), even in the absence of typical skin involvement.
a. Hypotension defined as a decrease in systolic BP greater than 30% from that person's baseline
b. Excluding lower respiratory symptoms triggered by common inhalant allergens or food allergens perceived to cause “inhalational” reactions in the absence of ingestion.
c. Laryngeal symptoms include: stridor, vocal changes, odynophagia.
d. An allergen is a substance (usually a protein) capable of triggering an immune response that can result in an allergic reaction. Most allergens act through an IgE-mediated pathway, but some non-allergen triggers can act independent of IgE (for example, via direct activation of mast cells).

PEF, Peak expiratory flow; BP, blood pressure.

activated in non-immunological anaphylaxis (3).

Anaphylaxis- Laboratory Values

Anaphylaxis is a clinical diagnosis and laboratory tests are not expected for treatment. However, the importance of laboratory tests increases in hypotension and a shock table which occurs without urticaria or angio-oedema (3). The measurement of serum/plasma triptase, plasma histamine, and histamine and histamine metabolites in 24-hour urine at the time of anaphylaxis may be of help in supporting the diagnosis. The best time interval for taking the serum triptase measurement is 15 mins after the onset of anaphylactic symptoms and at 3 hours at the latest (21). Comparison should be made with the triptase level measured 24 hours after the complete recovery of anaphylaxis (basal triptase). An increase of 20% + 2ng/ml in the triptase level measured during the reaction compared to the basal level supports the diagnosis of anaphylaxis. If the level measured in the acute phase and the basal triptase level are >11.4 ng/ml, mastocytosis or clonal mast cell disorders should be investigated (22, 23). In anaphylaxis cases, the blood histamine level increases within 5-10 mins and returns to normal within 30-60 mins. However, the measurement and use of this in practice for diagnostic purposes is extremely difficult (24).

One of the mediators helpful in diagnosis is platelet activating factor (PAF), which has been shown to have a better correlation with the severity of the reaction than triptase and histamine. However, as increasing PAF at the time of anaphylaxis is rapidly metabolised by PAF-acetyl hydrolase (PAF-AH), it is difficult to use it in the diagnosis (25).

Anaphylaxis Differential Diagnosis

The conditions most frequently confused with anaphylaxis are acute asthma, syncope and anxiety/

Table 2. The differential diagnoses of anaphylaxis

Common disorders:
•Asthma Attack
•Vasovagal Syncope
•Anxiety/Panic Attack
•Acute generalized urticaria and /or angio-oedema
•Foreign Body Aspiration
•Cardiovascular Diseases (myocardial infarct, pulmonary emboli)
•Neurological Event (Cerebrovascular event)
Flushing Syndromes:
•Carcinoid Syndrome
•Thyroid Medullar Carcinoma
•Premenopause
Postprandial Syndrome:
•Scombroidosis
•Chinese Restaurant Syndrome (monosodium glutamate)
Shock:
•Hypovolemic
•Septic
•Cardiogenic
•Distributive
Endogenous over-production of histamine
•Mast cell activation syndromes
•Basophilic leukaemia
•Hydatic cyst
Inorganic Diseases:
•Vocal cord dysfunction
•Hyperventilation
•Psychosomatic
Others:
•Non-allergic angio-oedema
-Hereditary angio-oedema
-ACE inhibitor-related angio-oedema
•Systemic Capillary Leakage Syndrome
•Red Man Syndrome (vancomycin)
•Pheochromacytoma

Table 3. Common Mistakes in Treating Anaphylaxis

1) Not administering adrenalin immediately
2) Not administering adrenalin IM or from the appropriate place (anterolateral of the thigh).
3) Administering anti-histamine and corticosteroid as the first drug instead of adrenalin
4) Moving the patient into a sitting or standing position too soon.
5) Discharging the patient before completing at least 6-8 hours observation
6) Administering salbutamol as the first drug instead of adrenalin when there is wheezing

panic attack. Severe asthma may cause diagnostic confusion because wheezing respiration, cough and shortness of breath may be seen in both asthma and anaphylaxis. However, itching, urticaria, angio-oedema, abdominal pain, and hypotension are not expected in acute asthma. Anxiety-Panic attack may also be confused with anaphylaxis. In both conditions, symptoms may be seen such as a feeling of impending disaster, shortness of breath, flushing, tachycardia and gastrointestinal symptoms. However, urticaria, angio-oedema, wheezing respiration and hypotension are not observed during anxiety/panic attack. There may be confusion with syncope because hypotension is seen in both conditions, but in syncope, patients relax when lying down and generally have cold sweats. The differential diagnoses of anaphylaxis are summarised in Table 2 (26).

Anaphylaxis Treatment

As the heart and respiration can stop within minutes during anaphylaxis, treatment must be applied rapidly

Table 4. Emergency Management of Anaphylaxis

Diagnosis is made clinically.

*The most commonly seen symptoms are cutaneous (eg, sudden onset of generalised urticaria, angio-oedema, flushing, oedema). However, 10 to 20% of patients have no skin findings.

*Dangerous signs: Rapid progression of symptoms, respiratory problems, (eg, stridor, wheezing respiration, dyspnea, persistent cough, cyanosis) vomiting, abdominal pain, hypotension, rhythm disorder, chest pain, collapse

Acute Management:

*Adrenalin is the first and most important treatment in anaphylaxis. There is no absolute contra-indication for adrenalin in anaphylaxis.

*Airway: A patient with evidence of an approaching airway obstruction because of angio-oedema must be urgently intubated. The intubation may be difficult and must be made by an experienced clinician. A cricothyrotomy may be necessary.

*The following are applied immediately and simultaneously.

-IM adrenalin: 0.3-0.5 mg is injected into the muscle, preferably to the mid-lateral thigh. It can be repeated every 5-15 mins (or more often) as necessary. If adrenalin is injected IM immediately, most patients respond after one, two, or maximum three doses. If symptoms do not respond to adrenalin injections, an IV adrenalin infusion is administered.

-Place patient in recumbent position, if tolerated, and elevate lower extremities.

-Oxygen: Give 8 to 10 L/minute via facemask or up to 100% oxygen, as needed.

-Normal saline rapid bolus: Hypotension is treated with IV rapid infusion of 1-2 litres. It can be repeated as necessary.

-Salbutamol: For bronchospasm resistant to IM adrenalin, salbutamol is given at 2.5 -5mg in 3mL saline via a nebuliser, or with a measured dose inhaler with 2-3 inhalations. It can be repeated as necessary.

*** Adjuvant treatments:**

-H1 antihistamines: Only to eliminate urticaria and itching, cetirizine 10mg IV (in 2 mins) or diphenhydramine 25-50 mg IV (5 mins) is administered.

-H2 antihistamine: Famotidine 20 mg IV (given in 2 mins).

-Glucocorticoid: Methylprednisolone can be given as 125 mg IV.

-Monitoring: Continuous noninvasive hemodynamic monitoring and pulse oximetry monitoring should be performed. Urine output should be monitored in patients receiving IV fluid resuscitation for severe hypotension or shock.

Treatment of refractory symptoms:

*Epinephrine infusion: For patients with insufficient response to IM adrenalin and IV saline, a continuous adrenalin infusion is started with an infusion pump at 0.1 mcg/kg/min.

* Vasopressors: Some patients may need a second vasopressor in addition to adrenalin.

* Glucagon: Patients using beta blockers may not be able to respond to adrenalin, and can be given 1 -5 mg IV glucagon within 5 mins, followed by 5-15 mcg/min infusion. Rapid administration of glucagon may cause vomiting.

Figure 1. Adrenalin Auto-Injector

immediately after diagnosis (27). Before starting treatment, vital signs must be evaluated, airway must be provided and contact with the allergen must be stopped. The patient should be positioned supine with the legs above the level of the heart and oxygen should be provided with a mask at 8-10 L/min. Adrenalin is the first and most important drug that should be given in treatment. It should be administered intramuscularly (IM) to the antero-lateral of the thigh (to the vastus lateralis muscle) at an adult dose of 0.3-0.5mg. When symptoms continue it can be repeated several times at 10-15-min intervals. If no response is obtained to IM administered adrenalin, an infusion of adrenalin can be administered intravenously (IV). Rapid IV fluid treatment should be given of 10-20 mk/kg in 10 mins. The common mistakes made in anaphylaxis treatment are shown in Table 3 (3). As the second stage in anaphylaxis treatment, antihistamines are given after adrenalin. The use of antihistamines is safe and they should be administered slowly as IM or IV (diphenhydramine 50 mg). If bronchospasm is determined, 2.5-5 mg salbutamol is given with a nebuliser, or if there is no nebuliser available, salbutamol is given as 4 puffs from an inhaler. If necessary, this procedure can be repeated 3 times at 20-min intervals. Methylprednisolone of 2mg/kg (maximum 125 mg) can be given IM or IV (3). In patients with bradycardia, rather than tachycardia known during anaphylaxis, and in those where a sufficient response is not obtained to adrenalin treatment, the patient must be asked if they are using beta blockers. In patients with a history of beta blocker use, glucagon must be administered, as beta receptors have inotropic and chronotropic effects with an external mechanism. In adults, glucagon infusion can be started with 1-5 mg IV in at least longer than 5 mins, followed by 5-15 mcg/min (28). The emergency methods applied to adults in anaphylaxis are shown in Table 4 (29).

Figure 2. Allergy Wristband

Anaphylaxis Education

Despite all the protective methods applied, anaphylaxis can recur. Therefore, the most important point to be made in patient education is the prescription of the Adrenalin Auto-Injector (AAI) (Figure 1), and to teach when and how it is to be used. The emergency treatment plan, anaphylaxis education and carrying identification, are other important points in the training (29). To eliminate concerns about the use of adrenalin, it must be explained that no other drug is life-saving and adrenalin should be used without hesitation when necessary (30). It must also be emphasised that a subsequent attack can be completely different from the one before, and the patient must always carry the AAI with them (3). Every patient with a history of anaphylaxis must carry identification with a telephone number to be contacted in case of emergency, and a list of triggering agents. This can be in the form of a wristband or ankle band (Figure 2), or as a card carried in the wallet at all times (3).

CONCLUSION

It must not be overlooked that several situations can

lead to anaphylaxis. Recent studies have shown that anaphylaxis is not a diagnosis that is predominantly considered by physicians and healthcare personnel. It can be considered that the awareness of anaphylaxis of both healthcare personnel and patients can be increased in the near future through training and scientific studies. Anaphylaxis diagnosis can be made with evaluations including a detailed anamnesis and clinical suspicion. Finally, the importance of the efficacy of adrenalin in the treatment must be emphasized.

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