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ALLERGIC REACTIONS IN INTENSIVE CARE UNIT

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Abstract

Allergic reactions are adverse effects as a result of the action of a certain antigen that causes an immune reaction. An antigen can be a drug, biological agent, toxin, chemical substrate or other substance to which a patient is exposed,and that exhibits a local or systemic reaction. The most severe reaction of hypersensitivity is anaphylaxis. In the process of causing anaphylaxis, a reaction is life-threatening and patients usually have skin, respiratory and gastrointestinal symptoms.

In certain number, allergic reactions also appear in patients in an intensive care unit. Recognizing and establishing a diagnosis in critically ill patients is quite serious challenge for two reasons: these patients have similar symptoms from another medical cause, and because they are usually sedated and on mechanical ventilation, which can mask the clinical picture. Treatment begins with quick recognition, diagnosis.and removal of the causative agent. The first step is to secure theairway. The second one is fluid resuscitation and blood pressure maintenance with or without vasopressors. The third part is pharmacological action on the resulting immune reaction.

Key Words:*allergic reactions, anaphylaxis,drugs, hypersensitivity.*

Introduction

Allergic reactions are side effects caused by a certain antigen that causes an immune reaction. An antigen can be a drug, biological agent, toxin, chemical substrate or other substance to which a patient is exposed, and that exhibits a local or systemic immune-predicted reaction.

The most severe reaction of hypersensitivity is anaphylaxis. In the process of causing an anaphylactic reaction which is life-threatening, it is usually manifests itself with skin, respiratory and gastrointestinal symptoms.

Milder forms of hypersensitivity reactions are more common with lower involvement of organ systems.

In the general population, the incidence of anaphylactic reactions ranges from 10 to 20 per 100,000 patients per year (1,2).

Side effects of the drug occur in 25% of hospitalized patients, but immunological allergic reactions are less than 15%.

In the intensive care unit, allergic reactions are difficult to diagnose because patients are sedated and on mechanical ventilation. In a critically ill patient who is intubated and sedated, alrergic reactions are difficult to be distinguished from signs of septic shock if the main clinical

manifestation is hypotension. Even when the diagnosis of anaphylactic shock is established, identifying the causative agent is a problem.

Pathophysiology of Allergic Reactions

Hypersensitivity reactions can involve all important components of the immune system, namely: cellular elements, immunoglobulins, complement and cytokines. The antigen reacts with cellular elements or immunoglobulins, causing the release of chemical mediators, which on the other hand include vasoactive amines (histamines, proteases), inflammatory leukotrienes, prostaglandins, platelet activating factor and the complement system. These mediators then interact with organ systems and cause clinical symptoms of allergic reaction and anaphylaxis (3).

Mediators of Allergic Reactions

Histamine is a low molecular weight amine stored in the granules of mast cells and basophils. It is released as a result of the action of a specific antigen.

When released, histamine increases capillary permeability, causes bronchospasm and vasospasm, and causes hypersecretion of mucous glands.

When released systemically, histamine acts within 1-2 minutes and is rapidly metabolized within 15 minutes.

Leukotrienes are metabolites of arachidonic acid, and also cause bronchospasm and vasospasm. Leukotrienes C4, D4 and E4 are produced by mast cells and basophils. These leukotrienes are more potent than histamine and have a longer-lasting effect on smooth muscles. Prostaglandins and thromboxane, also metabolites of arachidonic acid, are produced by fat cells. Prostaglandin D2 is the primary prostaglandin produced by mast cells and is a potential bronchoconstrictor and causes platelet aggregation and lysis (3).

Immunological Potential

The immunological potential of the antigen depends on the size. Low molecular weight antigens require binding to a specific carrier protein to be recognized by the immune system. In the case of penicillin G (356mol weight), it binds to circulating serum proteins in the form of a hapten which in turn has a strong immunological potential.

In the case of a biological agent, the immunological potential depends on the quality and type of the material.

Classification of Allergic Reactions

Type I- Allergic reactions mediated by IgE,

Type II- Cytotoxic hypersensitivity,

Type III- Allergic reaction with deposition of an immune complex,

Type IV- T-cell mediated allergic reaction.

Clinical Manifestations of Allergic Reactions in an Intensive Care Unit

Anaphylactic Reaction

An anaphylactic reaction is defined as a serious allergic reaction mediated by IgE. Anaphylaxis occurs suddenly, involves several organ systems, and can cause death (1,2). Clinical manifestations of anaphylaxis include urticaria, bronchospasm, hypotension, angioedema, laryngospasm, nausea, vomiting and others. In patients who have hypotension caused by anaphylaxis, they have a clinical picture of distributive shock, and we usually define it as anaphylactic shock.

Inflammatory mediators, including histamine, cause vasodilation and increased vascular permeability. The anaphylactic reaction occurs about 30 minutes after exposure to the allergen. The risk of death is greatest in the first few hours, especially if it is not promptly recognized and treated. If death occurs, it is usually the result of asphyxia from airway obstruction and collapse.

In the intensive care unit, it is challenging to recognize a patient with anaphylactic shock.

The diagnosis of anaphylactic reactions in critically ill patients in the intensive care unit is a real challenge. The first reason is that the symptoms that are a sign of an allergic reaction are present in critically ill patients as a result of other causes of the primary disease. The second reason is that the patients who are sedated on mechanical ventilation do not manifest the overall clinical specific picture of an allergic reaction. The occurrence of anaphylaxis in a sedated patient is mostly with altered symptomatology. If there is no dermatological reaction, it is very difficult to recognize it. The most common causes of anaphylaxis in intensive care units are drugs, biological material, vaccines, food, anesthetics, latex and less often some other environmental factors. In hospitalized patients, drug-induced anaphylaxis accounts for about 6% of all drug-induced side effects.

Anaphylactic reactions differ among themselves by the mechanism of occurrence and the mediators that participate in the process. These reactions are mostly caused by the activation of IgE as mediators, while the reactions caused by non-IgE mediators are created as a result of the release of mediators from mast cells and basophils. However, the symptoms and treatment of both types of allergic/anaphylactic reactions are the same.

Dermatological Symptomatology

Skin reactions are the most common hypersensitivity reactions. The most often these phenomena are mild and resolve spontaneously. Less commonly, some skin manifestations may progress and develop into potentially life-threatening reactions, such as toxic epidermal necrosis or Steven-Johnson syndrome. The pathogenesis of these phenomena is unclear, but it is assumed that they occur with the mediation of T-cells. The symptoms of these life-threatening dermatological reactions are delayed and are usually several days or weeks after exposure to the antigen. They are characterized by an acute macular rash and ultimately necrosis of the skin and mucous membranes.

Many of the patients have eye complications and half of those who survive have permanent complications (3).

Respiratory Symptomatology

Respiratory symptoms that are caused by an immune mechanism are usually part of complex phenomena, such as anaphylaxis, but they can also be an independent phenomenon. Acute

asthmatic reaction and rhinitis occur as reaction to hypersensitivity to drugs (aspirin, non-steroidal anti-inflammatory drugs), food additives or other allergens from the environment.

Allergic Vasculitis

Allergic vasculitis occurs as a result of deposition of immune complexes in small blood vessels. Clinical findings include skin lesions, purpura, joint pain, fever, urticaria, lymphadenopathy, etc. These phenomena are followed by elevated sedimentation. The systemic reaction is usually prolonged (1-2 weeks).

Vasculitis can involve multiple visceral organs, such as kidneys, lungs, liver, joints and central nervous system.

Very rarely the clinical picture can be severe, as glomerulonephritis, intestinal nephritis and various degrees of hepatocellular injury can occur as complications.

The most common cause is drugs: allopurinol, beta lactam antibiotics, sulfonamide, thiazide diuretics and phenytoin.

Angioedema

Angioedema is defined as a condition of swelling of the mucosa or submucosa, involving the larynx or pharynx. The swelling can spread to the mucous tissue of the face, gastrointestinal tract, lower limbs and genitals.

Angioedema can be the result of an allergic or non-allergic reaction. The life-threatening form of angioedema can be of genetic origin (C1 esterase inhibitor deficiency) or caused by the action of an antigen. The most common reasons that cause the release of bradykinin, which is the main mediator in the occurrence of angioedema, are ACE inhibitors. This type of drug-induced angioedema is mediated IgE type I hypersensitivity reaction that begins rapidly after drug administration. The incidence of angioedema caused by ACE inhibitors in the general population is about 0.1 to 0.7%. Differentiating between allergic and non-allergic angioedema in clinical practice is not always necessary since the therapy is the same.

Providing an airway is the main goal in angioedema. If there is a life-threatening obstruction, immediate tracheotomy is recommended. Out of the drugs that can be given at first, the choice is epinephrine, intravenously or in the form of an aerosol. Corticosteroids or antihistamines can be given, but they are not fast acting. Removal of the antigen is of crucial importance.

Acute Interstitial Nephritis

The acute interstitial nephritis is a form of allergic reaction that attacks the kidneys. Some drugs are described in the literature as potential triggers, and some of them are used in the intensive care unit. These include penicillin, proton pump inhibitors and nonsteroidal anti-inflammatory drugs.

It is assumed that the drug acts as an antigen/hapten mimicking a renal antigen that triggers the formation of an immune complex which, on the other hand, is deposited in the renal parenchyma. The traditional triad of symptoms, fever, rash and joint pain is described for the first time in methicillin-induced glomerulonephritis. Other non-specific symptoms are pain and hematuria (4). The only way to make a definitive diagnosis is a kidney biopsy, a procedure that has its own risks. A kidney biopsy is indicated only in very severe cases when discontinuation of the drug

considered to be the antigen/causing agent does not lead to improvement and if all other causes of renal failure are excluded.

Acute glomerulonephritis as an allergic phenomenon usually occurs after the administration of penicillin antibiotics. Other preparations (piperacillin), cephalosporins (ceftriaxone, cefotetan) and vancomycin are also possible causes of this allergic reaction. The onset of clinical symptoms of acute glomerulonephritis caused by drug allergy can range from several days to several weeks (5). The most often, this form of allergic glomerulonephritis is reversible, and the symptoms subside slowly over several weeks and months.

Proton pump inhibitors are the second possible cause of allergic acute glomerulonephritis. In a review study, 60 cases were described, out of which 59 were proven by kidney biopsy (6).

Corticosteroids are recommended as therapy for allergic glomerulonephritis. A dose of 1mg/kg of prednisone per day for 1-2 months is prescribed as therapy. Because of the possible side effects, corticosteroid therapy is acceptable only in very severe forms that do not improve after exclusion of the causative drug.

Therapy for Allergic Reactions

In the therapeutic strategies for allergic reactions, the most important thing is the rapid recognition and removal of the possible antigen/causing agent and supportive therapy.

Treatment for Anaphylaxis

The most important part of treatment is quickly establishing a secure airway. After providing an airway, adequate rehydration with fluids and maintenance of blood pressure, if necessary, with vasopressors is recommended. The third part is the pharmacological effect on the immune process in the already occurring allergic reaction.

The drug of choice is epinephrine at a dose of 0.3-0.5mg intramuscularly for adults and 0.01mg/kg for children, and this dose can be repeated every 5 minutes if necessary (7).

Fluid resuscitation should be started quickly and aggressively. If it is not possible to maintain the blood pressure, the inclusion of a vasopressor is recommended, and the most appropriate choice is vasopressin in case of an epinephrine-resistant reaction. Vasopressin has been described in the literature as quite effective in the case reports of anaphylactic shock (8).

The second recommended line of medication is corticosteroids and antihistamines. Systemic administration of corticosteroids has not been shown to be useful in the acute phase because the action of these drugs is delayed, after 4-6 hours. Corticosteroids may be useful in patients with bronchospasm, a history of asthma and in patients with severe dermatologic reactions. Corticosteroid therapy and antihistamines are not helpful and are not recommended in non-immune angioedema.

Conclusion

Allergic reactions to drugs are manifested by a different clinical picture. In certain number, they also appear in patients in an intensive care unit. Recognizing and establishing a diagnosis in critically ill patients is quite a serious challenge for two reasons: these patients have similar symptoms from another medical cause and because they are usually sedated and on mechanical ventilation, which can mask the clinical picture.

Treatment begins with quick recognition, diagnosis, and removal of the causative agent. The first step is to secure an airway. The second is fluid resuscitation and blood pressure maintenance with or without vasopressors. The third part is pharmacological action on the resulting immune reaction.

Quick recognition and appropriate therapy lead to success, saving the patient's life and withdrawal of symptoms.

References:

1. Sampson HA, Muñoz-Furlong A, BockS A, et al: Symposium on the definition and management of anaphylaxis: Summary report. J Allergy ClinImmunol 2005 Mar;115:584–591.
2. Sampson HA, Munoz-FurlongA, Campbell RL,et al:Second symposium on the definition and management of anaphylaxis: Summary report. AnnEmergMed2006;47:373–380.
3. Kanji S, Pharm D, Chant C, et al: Allergic and hypersensitivity reactions in the intensive care unit. Crit care Med 2010 Vol.38. No. 6 (Suppl.): 162-168.
4. Kodner CM, Kudrimoti A:Diagnosis and management of acute interstitial nephritis. Am Fam Physician 2003;67:2527–2534.
5. Plakogiannis R, NogidA: Acute interstitial nephritis associated with coadministration of vancomycin and ceftriaxone:Case series and review of the literature. Pharmacotherapy 2007;27:1456–1461.
6. Sierra F, Suarez M, Rey M, et al: Systematic review: Protonpump inhibitor-associated acute interstitial nephritis. Aliment Pharma-colTher2007;26:545–553.
7. Sheikh A, ShehataYA ,BrownSGA, et al: Adrenaline for the treatment of anaphylaxis: Cochrane systematic review.Allergy2009;64:204–212.
8. Schummer C,Wirsing M, Shummer W:The pivotal role of vasopress in inrefractory anaphylactic shock. Anesth Analg 2008;107:620–624.