Ministry of Health of Ukraine
Poltava State Medical University

Approved"
at the meeting of the Department of
of Internal Medicine No. 3, Phthisiology
“___”_____20___
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Minutes № from
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METHODOLOGICAL RECOMMENDATIONS FOR CONDUCTING AND PREPARING FOR PRACTICAL CLASSES

Academic discipline	Clinical immunology and allergology
*Module **4***	Clinical immunology and allergology
Content module	Clinical immunology and allergology
Topic №9	Atopy and allergy. Immune mechanisms of allergy development. Laboratory allergy diagnostics. Non-reactive manifestations of allergy. Principles of treatment of allergic pathologies
Course	5
Hours	2

Poltava 2023

Methodological recommendations for the practical training for independent work of students in preparation for the practical training and during the class were prepared by:
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Methodological recommendations were re-approved at the meeting of the Department of Internal Medicine of Internal Medicine №3 with Phthisiology_____
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Relevance of the topic.

In recent decades, the number of people with allergic diseases has increased in all countries. It is known that today 10-20% of all people suffer from them. The structure of morbidity has certain differences in childhood and adulthood: allergic skin lesions predominate among allergic diseases in the first years of life, while allergic diseases of the ENT and respiratory system prevail in adolescents and adults. It should be recalled that outwardly allergic manifestations in many cases (up to 40-50% in early childhood) may have a pseudo-allergic genesis.

Since the first doctors to whom patients visit are district (family) doctors, the latter should be able to make a differential diagnosis of allergy and pseudoallergy, to further determine the tactics of managing the patient or referring him (in severe cases) to the appropriate specialists. To conduct differential diagnosis and subsequent prescription of adequate therapy of diseases, graduates of medical higher education institutions should have knowledge of the pathogenesis, clinical course, modern diagnostic methods in allergic and pseudoallergic diseases.

Specific objectives:

To know:

1. Classification and immunopathogenesis of different types of allergic reactions.

2. Mechanisms of development of pseudoallergic diseases.

3. Principles of diagnosis and differential diagnosis of allergy and pseudoallergy based on clinical and anamnestic methods.

4. Basic immunological and allergological criteria for the differential diagnosis of allergy and pseudoallergy.

5. The main groups of drugs used in these diseases, mechanism of action, indications and contraindications.

Be able to:

1. Collect allergic anamnesis.

2. Conduct differential diagnosis of allergy and pseudoallergy based on anamnestic data.

3. Draw up a plan for additional examination using allergological and immunological methods.

4. Prescribe adequate therapy, taking into account the allergic or pseudoallergic genesis of the disease.

To master:

1. Methods of collecting allergic anamnesis, taking into account hereditary burden, the influence of adverse factors during the ante-, intra- and postnatal periods.

2. Methods of clinical examination of patients with allergic and pseudoallergic diseases.

Theoretical questions for the practical session:

1. Give the classification by Jell and Coombs. The mechanism of development of each type of reaction.

2. What are the current views on the mechanism of development of atopic diseases?

3. What are the etiology and pathogenesis of pseudoallergy, types of pseudoallergic reactions?

4. How do pseudoallergic reactions develop by the histamine mechanism?

5. What are the reasons for the development of pseudoallergic reactions due to inadequate activation of the classical and alternative complement pathways?

6. What are the mechanisms underlying pseudoallergy caused by impaired fatty acid metabolism?

7. What are the principles of diagnosis and differential diagnosis of atopic and pseudo-atopic reactions?

8. What are the criteria for the differential diagnosis of allergic and pseudoallergic urticaria and atopic and pseudoatopic dermatitis?

9. What are the criteria for the differential diagnosis of atopic and pseudo-atopic bronchial asthma?

10. What are the criteria for the differential diagnosis of allergy and pseudo-allergy to drugs?

11. What are the criteria for the differential diagnosis of Quincke's edema and hereditary angioedema?

12. What are the principles of treatment of allergic diseases?

Types of reactions (according to Coombs and Jel classification), immunopathogenesis of allergic diseases

A true allergy is an immunopathological reaction of the body to substances of antigenic or hapten nature (allergens), accompanied by damage to the structure and function of cells, tissues, organs and body systems.

There are 3 stages of allergic reactions: immunological, pathochemical and pathophysiological. The most common classification of allergic reaction types is Coombs and Jell, based on the pathogenetic principle. According to this classification, there are 4 types of reactions that differ in immune mechanisms. It is now believed that allergic diseases are predominantly type I, with autoimmune diseases being more common in other types.

In recent years, it has become known that normal, protective immune reactions are based on the same mechanisms, and only with significant quantitative changes do qualitative disorders occur, leading to damage to the body's own tissues, i.e. pathological processes occur; in other words, allergy as a disease carries a new quality that is the result of quantitative changes that are not amenable to regulatory mechanisms.

Normally, type I reactions play a role in the protection of mucous membranes. Ig E is produced by plasma cells of the adenoids, tonsils, spleen, mucous membranes of the respiratory tract, stomach and intestines. It targets relatively safe environmental antigens that penetrate the mucous membranes. When infectious agents and other foreign substances penetrate the barrier formed by Ig A, they are bound by specific Ig E on the surface of basophils and mastocytes. This results in degranulation of tissue basophils, release of biologically active substances with chemotactic activity, and local inflammation. Another important biological role of Ig E is protection against helminths (antibody-mediated cellular cytotoxicity).

In pathology, type I is atopic reactions (anaphylactic, immediate hypersensitivity reactions) associated with hyperproduction of total Ig E and production of specific Ig E to allergens. It should be recalled that the allergen must have the following properties: be genetically foreign, have a size of at least 10 kD, and be in a colloidal soluble state. It is well known that Ig E-T production is a T-dependent process. In atopic reactions, the function of type II T-helper cells, which produce interleukins (ILs), predominates: IL-4 and IL-13, which promote the switch of B-lymphocytes to Ig E production, and IL-5, which is a factor in eosinophil differentiation. The function of type I T-helper cells, which are mainly responsible for protection against intracellular pathogens, is reduced in atopy.

The development of this type of reaction requires the formation of specific Ig E and their fixation on mastocytes and basophils (which occurs during the first contact with the allergen). Re-entry of the allergen into the body leads to cross-binding of the allergen by two Ig E molecules fixed on the mastocyte or basophil. After that, the pathochemical stage begins, associated with the degranulation of basophils and mastocytes and the release of biologically active substances (BAS). There are acute (early) and late stages of atopic reactions. The following biologically active substances play a role in the development of the acute stage: histamine, heparin, serotonin, leukotrienes, chemotaxis factors of neutrophils, eosinophils, and others. In the late stage, the following are involved: platelet-activating factor, major basic protein, cationic protein, peroxidase, which are produced by eosinophils.

Type II cytotoxic reactions normally provide antimicrobial immunity, are involved in the elimination of tumour cells, cells with mutations, aging, etc. In pathology, Ig G and Ig M are produced to their own antigens, which are components of the cytomembrane or substances fixed on its surface. This type of reaction is the basis for the development of many autoimmune diseases, which are characterised by a local process. Complement and lysosomal enzymes play the most important role in the pathological stage of this type of reaction.

Type III - immunocomplex reactions, normally associated with the formation and subsequent elimination of immune complexes. In pathology, immunocomplex reactions are the formation of circulating immune complexes (antigen + antibody, represented by immunoglobulins of classes G and M) in the vascular bed with subsequent fixation on the cell membrane. Unlike type II antibodies, antibodies interact with soluble antigens rather than with antigens on the cell surface. Most often, the resulting immune complexes are deposited under the vascular endothelium. This mechanism is responsible for the development of serum sickness, autoimmune diseases such as glomerulonephritis, autoimmune vasculitis, etc. The main mediators involved in the pathochemical stage are complement and lysosomal enzymes.

Type IV - delayed hypersensitivity reactions mediated by the T-type immune system (type I T-helper). Normally, they are effective in tuberculosis, syphilis, leprosy, and many viral infections. In case of pathology, they can cause the development of contact allergic dermatitis, transplant rejection reactions, and the development of certain autoimmune diseases. The main mediators of this type of reaction are cytokines produced by type I T-helper cells: IL-2 and γ-IFN.

The most common type I diseases in children are atopic diseases. Atopy is a constitutional or congenital predisposition to the development of type I reactions. As

is well known, atopic diseases include atopic bronchial asthma, pollenosis, atopic dermatitis, urticaria, Quincke's edema, and others.

Mechanisms of pseudoallergic reactions.

Pseudo-allergic reactions are clinical analogues of allergy, but they do not have an immunological stage. The same biologically active substances play a role in the pathochemical stage of pseudoallergy as in true allergy. It should be remembered that biologically active substances are a biological connection between cells, without which the fight against the pathogen is impossible.

In childhood, pseudoallergic reactions are the most common, being clinical analogues of atopy, and therefore are often called pseudoatopic. They are based on the histamine mechanism of development. Its essence lies in an increase in the concentration of free histamine in biological fluids, which, when acting on the H-1 and H-2 receptors of target cells, leads to pathological consequences. An increase in histamine concentration can occur in several ways:

1.Histamine liberation mechanism. Various active factors that act directly on mastocytes and basophils, causing either their destruction and thus the release of mediators, or, acting on these cells through the appropriate receptors, activate them and thus cause the secretion of histamine and other mediators.

In the first case, the acting factors are called non-selective or cytotoxic, and in the second case, selective. Often, this distribution is related to the concentration (dose) of the active factor.

The list of medicines, food products and chemical additives that have a histamine-liberating effect is given in the Appendix (Table 1). Physical, chemical and other factors can also have a histaminoliberative effect.

2.The histaminopectic pathway. It is associated with disruption of histamine inactivation mechanisms. The main pathways of histamine inactivation are oxidative deamination, which is triggered by histaminase and nitrogen methylation in the ring.

One of the ways of inactivation is the binding of histamine to serum proteins, which is called histaminopexy. Reduced histamine inactivation can be genetically determined or develop as a result of chronic diseases of the digestive system. Under normal conditions, the body can cope with small fluctuations in plasma histamine concentration, but when the concentration increases (histamine liberation by drugs

(Table 5), food or ingestion of excessive amounts of histamine), clinical manifestations develop up to anaphylactoid shock.

3.A mechanism associated with a damaging intake of histamine in the body. It occurs most often when eating certain foods. The list of foods containing a large amount of histamine is also given in the appendix (Table 1).

4.The mechanism associated with dysbiosis. It is associated with an increase in the decarboxylating activity of the opportunistic pathogenic flora in dysbiosis. At the same time, there is an increase in the formation of the corresponding amines - histamine, phenylethylamine, tyramine - from histidine, phenylalanine, tyrosine.

Given that the pathogenetic mechanisms of allergy and pseudoallergy are different, a differential diagnosis of these conditions is necessary to prescribe adequate therapy.

A particular diagnosis can be assumed on the basis of clinical and anamnestic criteria and objective examination data, and paraclinical methods, including immunological and allergological tests, can confirm the diagnosis.

Allergological and immunological methods in the diagnosis

and differential diagnosis of atopy and pseudoatopy.

Paraclinical methods, as mentioned earlier, include allergological and immunological examination. The most important in the differential diagnosis of allergy and pseudoallergy are

- skin tests;

- determination of the level of total Ig E

- specific Ig E;

- interleukin levels (IL-4 and γ-IFN).

- It is possible to use a spontaneous and allergen-stimulated B-cell blast transformation reaction.

Patients with true atopy will have positive skin tests with allergens, increased levels of total Ig E and the presence of specific Ig E, increased levels of IL-4 and decreased levels of γ-IFN. These parameters in patients with pseudoatopia do not differ from those of healthy children.

The criteria for differential diagnosis between some atopic diseases and their pseudoatopic analogues are given below.

For allergy and pseudoallergy, the most widely used drugs are H1 receptor blockers. All antihistamines are divided into first-generation drugs: dimedrol, diazoline, suprastin, peritol, fencarol, tavegil, pipolphen, and second-generation drugs: Astemizole (Hysmanal), loratadine (Claritin), azelastine (Allergodil), terfenadine (Trexil), cetirizine (Zyrtec), and third-generation drugs: fexofenadine (Telfast) and desloratadine (Erius).

It is worth highlighting the widespread, not always justified, use of first-generation antihistamines by paediatricians and parents in the treatment of allergic and pseudoallergic reactions, various diseases, as well as some mistakes in their prescription.

Firstly, it should be borne in mind that not only histamine but also other biologically active substances play a role in the development of allergic reactions, and therefore drugs with only antipistamine activity may not be effective enough and usually reduce only acute allergic manifestations. Second- and third-generation antihistamines have broader anti-allergic activity.

Secondly, the physician should remember the groups of drugs based on their chemical structure (see the classification in the appendix). If a drug is ineffective or an allergic reaction to an antihistamine occurs, it is unacceptable to prescribe a drug of the same group.

Thirdly, histamine and antihistamines have an immunomodulatory effect because histamine receptors are located on subpopulations of T-lymphocytes: T suppressor-cytotoxic T cells and T helper cells. Immunotropism is mediated through H2 receptors on T-helper cells and modulates the formation of antibody-producing cells, depending on the influence of other factors that inhibit or enhance the immune response. In different concentrations, histamine can have an inhibitory effect on the production of certain interleukins, etc.

We have studied the effect of dimedrol on the immune response when used in pharmacopoeial doses. As it turned out, dimedrol causes a significant

immunosuppressive effect, followed by an increase in the body's sensitivity to histamine after its discontinuation.

Therefore, the prescription of antihistamines, especially with antibiotics (which are also known to have an immunosuppressive effect), should be justified.

Fourthly, long-term use of first-generation antihistamines is ineffective because they are highly addictive.

The disadvantages of first-generation antihistamines include the following:

1. By penetrating the blood-brain barrier and interacting with H3 receptors, they can, in addition to the sedative effect, cause a decrease in children's learning ability, decreased concentration, decreased cognitive functions, etc.

2. These drugs are non-selective H1 receptor blockers, therefore they can cause atropine-like effect, antiadrenergic and serotoninolytic effects.

3. They block H1 receptors for a short time (1.5-3 hours).

4. They develop addiction quickly (on the 10-12th day of administration).

Doctors should be aware that cinnarizine (stugerone) is an antagonist of the most important mediators of anaphylaxis, even preventing the development of anaphylactic shock.

Second-generation antihistamines are free from many disadvantages. They are non-sedative (except for cetirizine), bind selectively and strongly to H1 receptors, have a rapid onset of action (except for astemizole) and a long-lasting effect, and do not develop addiction.

It is worth remembering that terfenadine and astemizole can cause cardiotoxic effects.

The mechanisms of action of the second-generation drug, clarithromycin, are best understood.

1. Claritin is a calcium channel inhibitor.

2. It acts as a membrane stabiliser.

3. Inhibits the production and release of prostaglandin D2.

4. Inhibits the formation of adhesion molecules of various classes.

5. Inhibits eosinophil chemotaxis, their accumulation in mucous membranes, platelet aggregation.

6. It inhibits the formation of superoxide anion (i.e. it is an antioxidant)

7. Reduces vascular permeability.

Since second-generation drugs have certain disadvantages, third-generation drugs Telfast and Erius were created.

In case of pseudoallergy caused by inadequate enhancement of classical or alternative pathways of complement activation, the best effect in the acute period is provided by administration of C1-inhibitor.

In case of pseudoallergy associated with arachidonic acid metabolism disorder, discontinuation of the drug is etiotropic. In the future, patients are not recommended to use non-steroidal anti-inflammatory drugs, foods containing the food colouring tartrazine and medicines in yellow capsules.

It should be noted that only those reactions involving the same substances as in allergy are considered pseudoallergic. A separate group includes enzymopathies, which can be clinical analogues of atopy or pseudoallergy, but are caused by completely different mechanisms. An example is lactase deficiency, which is an enzymopathy but not a pseudoallergy.

Thus, in order to establish the diagnosis of an allergic disease and subsequently prescribe adequate therapy, the physician must know the etiology and immunopathogenesis, and conduct a differential diagnosis with pseudoallergic reactions and other conditions that may resemble allergy. The physician should choose treatment tactics based on knowledge of the disease pathogenesis and mechanisms of action of the drug, and prevent relapses. Additional materials provided below will also help future doctors in solving these problems.

TASKS FOR SELF-CONTROL

1.A 4-month-old boy from the first uncomplicated pregnancy, physiological delivery, is on artificial feeding since 2 months (hypogalactia in the mother). At 3 months of age, he suffered from acute bronchitis, was prescribed pecicillin intramuscularly for 7 days. A week after that, the boy developed dyspeptic disorders, and then a rash appeared on the milk mixture, which he was fed before the disease. The plan of laboratory examination should include everything except:

a) faecal analysis for dysbiosis

б) Ultrasonography of the abdominal cavity

c) determination of the level of total Ig E

d) determination of the level of specific Ig E

e) determination of the level of IL-1 and 6

The correct answer is e

2.A 3-year-old child was diagnosed with atopic dermatitis. The first manifestations appeared at the age of 6 months in the form of erythematous squamous rash after eating citrus fruits. Now, according to the mother, the child has a food allergy to "everything". Laboratory tests to be used for diagnosis must include:

a) determination of the child's HLA phenotype

b) determination of general and specific Ig E

c) determination of the level of interleukins -1 and 6

d) determination of the level of interleukin-3

e) determination of the level of T- and B-lymphocytes

The correct answer is b

3.A boy was delivered to the emergency department with complaints of edema that appeared on the face after tooth extraction and within 2 hours spread to the neck, chest, upper extremities. The swelling was pale and dense. The condition did not improve after the paramedic administered Dimedrol and No-Spa. Possible causes of edema development:

a) immediate allergic reaction

b) delayed allergic reaction

c) arachidonic acid metabolism disorder

d) deficiency of C 1 inhibitor

e) reduction of histaminopexy

The correct answer is d

4.The girl is 5 years old. Allergic anamnesis is not burdened. She was referred for X-ray examination with suspicion of vesicoureteral reflux. After administration of radiopaque iodine-containing substance, she became dizzy, had cold sweats, blood pressure decreased to 75/50 mmHg. Preliminary diagnosis:

a) anaphylactoid shock

b) anaphylactic shock

c) Jarisch-Hexheimer reaction

d) psychogenic reaction

e) serum disease

The correct answer is a.

5.A 7-year-old boy complained to a paediatrician about attacks of suffocation. They first appeared 2 years ago during a holiday in the village with relatives. Now the

attacks are observed after cleaning the premises. The mother has a family history of atopic dermatitis.

Objectively, there are scattered dry whistling wheezes against the background of weakened breathing. The most likely allergens that cause attacks of suffocation:

a) food

b) pollen

c) endogenous

d) epidermal

e) household

The correct answer is e.

6.An 8-year-old child was first diagnosed with moderate asthma a year ago. During skin prick testing, it was determined that the allergen is house dust mite Dermatophagoidus Pteronissimus. Which therapy will be etiopathogenetic:

a) administration of β2-adrenomimetics

b) administration of anti-leukotriene drugs

c) administration of inhaled corticosteroids

d) specific immunotherapy

e) administration of antihistamines

The correct answer is d.

7.An 11-month-old child was diagnosed with atopic dermatitis. It is known that the first manifestations occurred at 6 months of age when eating half a yolk of a chicken egg, and there was no reaction to a smaller amount. Later, the mother observed a dose-dependent reaction to yolk, carrots, and cheese. There are cases of reactions to

large amounts of tomato juice and honey in the family history. The most likely causes of a child's rash are

a) pseudoallergy, histamine variant

b) pseudo-allergy caused by fatty acid metabolism disorder

c) immediate allergic reaction

d) allergic reaction of immunocomplex type

e) delayed allergic reaction

The correct answer is a.

8. An 11-month-old child was diagnosed with atopic dermatitis. It is known that the first manifestations occurred at 6 months of age when eating half a yolk of a chicken egg, and there was no reaction to a smaller amount. Later, the mother observed a dose-dependent reaction to yolk, carrots, and cheese. There are cases of reactions to large amounts of tomato juice and honey in the family history. The examination plan should include all but:

a) Ultrasonography of the abdominal cavity

b) determination of the level of total Ig E

c) determination of the level of specific Ig E

d) determination of the level of circulating immune complexes

e) conducting a coprogramme and faecal analysis for dysbiosis

The correct answer is d