MANIFESTATIONS OF VARIOUS DISEASES AND CHANGES IN THE BODY IN CHILDREN SUFFERING FROM DRUG ALLERGY

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Summary: *It is characterized by polymorphic rashes in the form of erythema, target-shaped papules, which can progress to vesicular and bullous lesions, on the site of which erosions form. Rashes are mainly localized on the hands, feet, upper and lower extremities. Mucosal involvement may occur. Erythema multiforme is a polyetiological disease mainly based on hypersensitivity reactions to drugs or infection, but in some cases associated with other pathological conditions, in particular with Kawasaki disease [68]. Treatment of patients is based on the withdrawal of causative drugs or the treatment of existing infectious diseases. In some cases, the course is recurrent, which is due to unresolved antigenic stimulation.*

Key words: *drug allergy; multiform exudative erythema; Stevens-Johnson Syndrome; toxic epidermal necrolysis.*

1 . Multiform exudative erythema. It is characterized by polymorphic rashes in the form of erythema, target-shaped papules, which can progress to vesicular and bullous lesions, on the site of which erosions form. Rashes are mainly localized on the hands, feet, upper and lower extremities. Mucosal involvement may occur. Erythema multiforme is a polyetiological disease mainly based on hypersensitivity reactions to drugs or infection, but in some cases associated with other pathological conditions, in particular with Kawasaki disease. Treatment of patients is based on the withdrawal of causative drugs or the treatment of existing infectious diseases. In some cases, the course is recurrent, which is due to unresolved antigenic stimulation.Stevens-Johnson Syndrome. Many experts consider it as a severe form of exudative erythema multiforme, in which there is a large area of skin involvement in the pathological process in the form of polymorphic rashes, including the formation of bullae, ulcerations, with lesions of the mucous membranes, internal organs, with fever, severe malaise. Other researchers consider this syndrome as an independent disease, similar in genesis to the syndrome of toxic epidermal necrolysis. They consider both of these syndromes to be forms of abnormal necrotic reactions of the skin and mucous membranes to drugs and/or infections accompanied by detachment of the epidermis and epithelium. Historically, they were classified as forms of erythema multiforme exudative, but are now considered as different diseases.

Toxic epidermal necrolysis. This is a severe variant of drug allergy that proceeds with bullous skin lesions, with a mortality rate of up to 30%. Some authors consider Stevens-Johnson syndrome as its milder form. The differences are in the area of skin lesions and in the nature of skin changes. The onset of the disease is usually marked by a

sudden rise in temperature, malaise, followed by rashes that are painful to the touch. Blisters then begin to form, and the classic Nikolsky sign appears, in which gentle lateral pressure causes the epidermis to shed. Histologically, this corresponds to widespread apoptosis of keratinocytes with separation between the dermis and epidermis. The mucous membranes of the mouth and genital organs, as well as the intestines and eyes, are involved in the process, which sometimes leads to blindness. These reactions are immune-mediated, and HLA associations with specific drugs have been described. Skin manifestations are mainly caused by cytotoxic T cells, however, other cells can play an important role in the formation of this syndrome. Among the main molecules that mediate toxic damage to keratinocytes both in this syndrome and in Stevens–Johnson syndrome, granulosin, tumor necrosis factor, and some other molecules are of particular importance. Their determination is proposed as diagnostic tests in the management of patients with these diseases.In addition to the skin lesions described above, other skin reactions to drugs are possible:

photodermatitis — erythematous rashes on open areas of the body, formation of vesicles, bullae is possible;the Arthus-Sakharov phenomenon is a local allergic reaction in the form of an infiltrate, abscess; erythema nodosum - red subcutaneous nodes, localized mainly on the anterior surface of the legs, may be accompanied by low-grade fever, malaise, arthralgia and myalgia;allergic vasculitis - symmetrical rashes that leave long-term pigmentation, usually localized in the lower third of the legs, on the ankles, buttocks;allergic contact dermatitis - erythema, edema appear at the site of drug exposure, vesicles, bullae may appear.Systemic and organ lesions in drug allergy. As mentioned above, despite the fact that the main target organ in drug allergy is the skin, and other organs may be involved in the pathological process, systemic effects are also possible. Anaphylaxis. This is a serious, life-threatening, generalized or systemic hypersensitivity reaction. In clinical practice, there are conditions similar in clinical picture, called non-allergic anaphylaxis. Anaphylactic shock is one of the most severe life-threatening manifestations of anaphylaxis in response to contact with an allergen (drug), accompanied by severe hemodynamic disorders that lead to circulatory failure and hypoxia of all vital organs. High lethality is noted.Serum disease. It is an acute allergic reaction that develops according to the immunocomplex mechanism, mainly in response to the introduction of heterologous sera, beta-lactam antibiotics, sulfonamides, cytostatics, NSAIDs, monoclonal antibodies. Symptoms appear 1-3 weeks after the start of treatment in the form of rashes (urticaria, maculopapular rash), fever, arthralgia (mainly large joints), lymphadenopathy. The duration of the disease ranges from several days to several weeks, depending on the severity.Drug fever. As a manifestation of drug allergy, it can be provoked, for example, by the use of betalactam antibiotics and other antimicrobial agents [84, 85]. It is characterized by a rise in temperature from subfebrile values to 39 ° C, from a short-term increase to a long-term one. It develops by an immunocomplex or cell-mediated mechanism. Unlike other fevers, the patient remains relatively well. In 2-3 days

after the withdrawal of the causally significant drug, the fever disappears. When the drug is re-administered, it resumes after a few hours.Features of the manifestation of drug allergic reactions in children. Most allergic reactions to drugs in children are associated with beta-lactam antibiotics, followed by NSAIDs, and less commonly macrolide antibiotics, sulfonamides, anticonvulsants, radiopaque agents, chemotherapy drugs, and other drugs. Risk factors for the formation of drug allergies in children are acute respiratory viral infections, especially in people predisposed to allergies, infection with herpes group viruses. Atopy, bronchial asthma, urticaria, atopic dermatitis are significant risk factors for the development of pediatric drug allergy. The main difficulty in its diagnosis is the differentiation of papular/morbilliform rash with possible viral exanthems, which are very common in this age group. Differential diagnosis is often difficult, it is proposed to evaluate the time relationship between the introduction of the drug and the onset of the reaction; it is important to take into account the condition of the skin, mucous membranes, the presence of fever, lymphadenopathy, changes in laboratory tests (eosinophilia of peripheral blood, increased levels of hepatic transaminases).In modern literature, it is recognized that the main clinical manifestations of drug hypersensitivity in children are various skin rashes and urticaria. Other manifestations are less common: allergic rhinitis, angioedema, attacks of bronchial asthma, stomatitis, hemorrhagic vasculitis, enteritis, fever, anaphylactic shock, Stevens-Johnson syndrome, Lyell's syndrome.The prevailing symptoms of drug hypersensitivity in children with bronchial asthma, atopic dermatitis, and dermatorespiratory syndrome are different. In children with bronchial asthma, the most common manifestations of drug allergy are attacks of bronchial asthma (35.6%), and urticaria (28.6%) is in second place in terms of frequency of occurrence; in 19.5% of children, allergy is manifested by various exanthems, in 11.7% of patients - in the form of angioedema. In children with atopic dermatitis, the most common manifestation of drug allergy is the exacerbation of atopic dermatitis (44.8%), the second place is urticaria and angioedema, detected with the same frequency (10%), the development of exanthems was noted in 16.8% of patients with this disease. In children with combined manifestations of skin and respiratory allergies, drug hypersensitivity reactions most often manifest as an exacerbation of atopic dermatitis (37.5%), angioedema (22.5%), less often - attacks of bronchial asthma (17.5%) and urticaria (15. 6%).Modern approaches to the diagnosis of drug allergyThe currently available scientific data, apparently, do not yet allow the formation of an exhaustive set of measures for the diagnosis of drug allergy. In this regard, methods of general clinical diagnostics are still of decisive importance, especially anamnesis data (allergological, pharmacological, family), general clinical examination with the identification of the main syndromes characteristic of drug allergies. In vivo tests and some in vitro biological tests can be used to diagnose some clinical and pathogenetic variants of drug allergy. However, the list of methods for the study of drug allergy certified for practical use is still rather scarce. Most of the methods have not gone beyond research projects.A carefully collected clinical

history is of fundamental importance in the diagnosis of drug allergy. The list of questions can be considered classic: it is important to establish the sequence of occurrence of symptoms, their duration and the relationship with the use of drugs, to which hypersensitivity reactions are presumably developed; assess the time interval between drug administration (last dose) and the onset of a reaction, the impact of discontinuation of treatment on the dynamics of symptoms, as well as the results of past use of other drugs of the same class. Information about the presence of allergic reactions and diseases in the patient's relatives, including reactions to drugs, is essential. Allergological and pharmacological history data give grounds to suspect the development of a drug allergy or, with a high degree of probability, to reject its presence in patients. It should be taken into account that from 1 to 10% of people with drug allergies have a syndrome of multiple drug intolerance (intolerance to three or more drugs that are neither structurally nor pharmacologically related). As for instrumental and laboratory research methods for drug allergy, most modern literature sources emphasize that their choice is determined by the characteristics of clinical manifestations, the severity of systemic and organ-specific symptoms, and the alleged immune mechanism of drug hypersensitivity reactions. In this regard, the list of methods includes a hemogram, x-ray examination of the lungs, examination of liver and kidney functions, determination of antinuclear and anticytoplasmic antibodies, specific immunological tests, and, in some cases, tissue biopsy. A thorough clinical study of patients with drug hypersensitivity allows assessing the nature, severity and danger of symptoms and conducting an adequate laboratory examination. This approach in a significant proportion of cases helps to ensure the correct diagnosis. In the acute phase of the resulting hypersensitivity reaction, it facilitates the decision to continue or stop the ongoing treatment, which could provoke the formation of a drug hypersensitivity reaction. If there is a risk of deterioration of the patient's condition, the suspected drugs should be discontinued immediately.It is also undoubted that a significant addition to the anamnestic and general clinical data in diagnosing the course of drug allergy are research methods for identifying the guilty antigen and biomarkers inherent in specific hypersensitivity reactions. Intensive research has been carried out in this direction in recent years. Allergological diagnosis can be carried out using in vivo and in vitro methods.In vivo methods (skin tests, provocative tests) are usually economically available and clinically informative. However, these tests can be performed no earlier than 4-6 weeks after stopping the drug hypersensitivity reaction, they require compliance with special conditions. This reduces their significance, as it does not allow them to be used in emergency diagnostics and therapy (post-factum diagnostics).In cases where it is not possible to exclude the diagnosis of drug allergy on the basis of anamnestic and clinical data, specific allergological diagnosis should be carried out in specialized centers. It allows you to establish a diagnosis and recommend alternative pharmacotherapy. Allergological diagnostics (skin testing, provocative tests) can be carried out only after the collection of allergic and pharmacological anamnesis data. The question of using an

allergological examination to confirm the allergic nature of drug hypersensitivity reactions most often arises in relation to antibiotics, NSAIDs, and anesthetics.Skin tests. Skin testing is a readily available method for diagnosing drug hypersensitivity. However, we did not find information on the presence of standard diagnostic allergens based on drugs in the literature (at least in Russia). Prick tests and intradermal tests are especially important in order to identify IgE-dependent mechanisms of drug allergy. Prick tests are recommended for the initial screening study. Intradermal tests can be performed with negative results of prick tests, they are quite informative in cases of development of immediate hypersensitivity reactions to beta-lactam antibiotics, heparin, in some cases - with delayed reactions. Patch tests (skin patch tests) and/or intradermal tests are performed to identify evidence of the possible development of T-cell-mediated delayed-type drug hypersensitivity reactions. In some cases, negative results of skin testing are due to the fact that it is not the drug itself that has immunogenic properties, but its metabolites. In these situations, drug challenge tests may be used to confirm the diagnosis. Medication provocative tests. They are the "gold standard" for identifying the drug that caused the development of hypersensitivity reactions. Provocative testing with a drug thought to be the cause of the side effect may confirm or exclude the diagnosis of a drug hypersensitivity reaction. Such tests are carried out no earlier than one month after the initial drug allergic reaction, only by specially trained personnel in specialized centers who are experienced in the early detection of hypersensitivity reactions and are ready to provide adequate medical assistance in case of life-threatening conditions. A contraindication for a provocative test is the presence of a life-threatening drug hypersensitivity reaction (anaphylactic shock, other systemic allergic reactions, severe skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, vasculitis). The methods of administration of the suspect drug during the provocation test are in principle the same as for the initial administration. At the same time, preference is given to the oral route of its administration, which is associated with a lower risk of hypersensitive drug reactions when the drug is administered per os. Biological tests in vitro. Great hopes are placed on the development of biological methods for diagnosing drug hypersensitivity reactions. Such methods are preferred for patients receiving simultaneous treatment with many drugs, as well as in the case of severe hypersensitivity reactions, when in vivo testing with drugs is contraindicated. Performing this type of research is safe for the patient and is possible at the peak of clinical manifestations. Among the in vitro tests, most of the methods introduced into clinical practice are based on the measurement of allergen-specific IgE antibodies to drug allergens. However, drug hypersensitivity IgEdependent reactions seem to be less common than, for example, delayed-type hypersensitivity reactions (mediated by T-lymphocytes). In addition, commercial kits for the determination of specific IgE are only available for a limited number of drugs, including amoxicillin, ampicillin, cefaclor, penicillin, insulin (bovine, porcine, human), adrenocorticotropic hormone, suxamethonium, and some other drugs. The absence of specific IgE to the

investigational medicinal products (negative test results) does not mean that immediate type drug allergy can be completely rejected in this case. Determination of drug-specific IgM or IgG may be warranted in cases of drug-induced cytopenia, hypersensitivity reactions to vaccines or dextrans. The sensitivity of these tests remains unexplored, and they are rarely used for diagnostic purposes.Among other (non-IgE) methods for diagnosing drug hypersensitivity in vitro, tests based on the detection of mediators released from various effector cells involved in the pathogenesis of drug hypersensitivity are used:determination of cysteine leukotrienes produced in vitro by isolated peripheral blood leukocytes after stimulation with a drug allergen; determination of the content of histamine, tryptase, granzyme in the blood serum, isolated from basophils and mast cells in cases of acute drug allergic reactions, including anaphylaxis; determination of cytokines released by lymphocytes.Currently, the possibility of using methods based on the study of cells involved in the immune response to diagnose drug hypersensitivity is also being actively studied. These methods include the following. Histamine release test from basophils with fluorimetric determination. It appears to be very promising and is currently being actively studied for its possible use in detecting hypersensitivity reactions to certain drugs.Basophil activation test. It is also one of the tests used to diagnose drug allergies. Basophils with a high affinity of their receptors for IgE are used as indicator cells in this test. Basophils activated by allergens in the presence of allergen-specific IgE express activation markers such as CD63 and CD203c as well as intracellular markers on their membranes. These changes in basophils can be detected by flow cytometry using specific monoclonal antibodies to activation markers. In the diagnosis of drug allergy, donor basophils, serum from a patient with a suspected drug allergy, and a causally significant antigen are used.Blast transformation reactions of lymphocytes with various drug allergens and some other methods. The immunological laboratory methods listed above, such as histamine release test from basophils (under the influence of a diagnosed drug), basophil activation test, cysteine leukotriene release test, lymphocyte activation tests, lymphocyte blast transformation reactions, can be very useful in some cases, but in everyday Currently, they are practically not used in clinical practice, since they are not yet standardized enough for the diagnosis of drug allergy. The informativeness of many of them has not been convincingly proven, and further development requires significant financial costs. It should be emphasized that it is currently not possible to finally confirm or exclude the presence of hypersensitivity to certain drugs only on the basis of in vitro tests. Test results should be interpreted in conjunction with the history and clinical findings. Recent advances in genetics have identified a number of HLA alleles associated with the formation of hypersensitive drug reactions, predominantly affecting the skin. For example, the identified associations between hypersensitivity to abacavir and HLA-B*57:01, as well as between carbamazepine-induced StevensJohnson syndrome and HLA-B*15:02 have been implemented in clinical practice - test systems have been

developed to identify predisposed persons, which makes it possible to implement in their relation the prevention of drug allergy to carbamazepines (restriction of their use).

Conclusion

Hypersensitive immune reactions to drugs, according to modern concepts, manifest themselves mainly as either immediate-type reactions (within 1-6 hours after taking the drug in various forms - from mild manifestations to life-threatening symptoms of anaphylaxis), or in the form of delayed-type reactions (from several hours to several days of taking the causally significant agent, manifesting clinically primarily in the form of exanthema). Specific diagnosis of drug allergy is carried out using in vivo tests (prick tests, intradermal testing, patch tests, provocative tests) and in vitro (determination of specific IgE to drugs, basophil activation tests, leukocyte blast transformation reactions, quantitative determination of cytokines and other proteins , such as granzyme and tryptase in peripheral blood). However, not all of these methods are currently available in real clinical practice; the list of commercial kits for diagnosing drug allergies is limited. When managing patients, it is important to rely on the data of anamnesis and general clinical examination, take into account the available information about the association of drug allergy and infection with herpes group viruses, especially in the child population, about the presence of a hereditary predisposition to the formation of some forms of drug allergy. Research funding and conflicts of interest. The study was not funded by any source and there are no conflicts of interest related to this study.

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