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Diseases Associated with Immune System Disorders in Allergic Diseases

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Annotation: Some proteins and many polypeptide drugs (e.g., insulin, therapeutic antibodies) can directly stimulate antibody production. However, many drugs act as haptens, covalently binding to serum or cellular proteins, including proteins that make up the major histocompatibility complex (MHC) molecules. This binding makes the protein-drug complex immunogenic, stimulating antibody production and/or a T-cell response to the drug. Haptens can directly bind to MHC class II molecules and directly activate T lymphocytes. Some drugs act as prohaptens. Prohaptens are converted to haptens through metabolic reactions; For example, penicillin itself is not an antigen, but its major degradation product, benzylpenicilloic acid, can combine with tissue proteins to form benzylpenicilloyl (BPO), a major antigenic determinant. Some drugs bind directly to and stimulate T cell receptors (TCRs); the clinical significance of nonhapten binding to the TCR remains to be determined (1).

Keywords: Autoimmune hemolytic anemia, Bullous pemphigoid, Cutaneous lupus erythematosus, Type 1 diabetes, Goodpasture syndrome, Graves' disease, Hashimoto's disease, Multiple sclerosis.

Introduction

In autoimmune conditions, antibodies are produced against endogenous antigens (autoantigens). The following types of hypersensitivity reactions can occur:

Type II: Cells containing antibodies, like any similar cells with foreign particles on their surface, activate the complement system, which leads to tissue damage.

Type III: Antigen-antibody complexes are sometimes involved in the mechanism of injury.

Category IV: T-cell-mediated injury.

Type I hypersensitivity is an immediate reaction involving the release of soluble anti-antigen mediators mediated by immunoglobulin E (IgE). Type I reactions are not involved in autoimmune diseases.

Specific autoimmune diseases discussed in the guide include:

Women are more likely to develop autoimmune diseases than men.

Mechanisms

Some mechanisms can be seen as the body's attack on itself:

Autoantibodies can become immunogenic if they undergo certain modifications.

Antibodies secreted in response to a foreign antigen can cross-react with normal autoantigens (for example, antibodies to streptococcal M-protein can cross-react with protein structures of human heart muscle).

Autoantigens normally secreted by the immune system can be implicated and cause an autoimmune reaction (e.g., systemic release of melanin-containing uveal cells after eye injury leads to sympathetic ophthalmia).

Research methods and materials

Autoantigens can undergo chemical, physical, or biological changes:

Chemical: Certain chemicals bind to proteins in the human body, making them immunogenic, which occurs in some cases of drug-induced immune hemolytic anemia.

Physical: For example, ultraviolet rays induce keratinocyte apoptosis and, accordingly, alter the immunogenicity of autoantigens, which leads to photosensitivity - this is how cutaneous lupus erythematosus occurs.

Biological: Using animal models, persistent infection with an RNA virus that integrates into host tissues biologically alters autoantigens and leads to an autoimmune condition resembling systemic lupus erythematosus.

Genetic factors

Autoantibodies are often detected in relatives of patients with autoimmune diseases. The specificity of autoantibodies in patients and their relatives is often, but not always, similar. In identical twins, if one twin has an autoimmune disease, the other twin is more likely to develop it (1).

Many autoimmune diseases have a polygenic etiology, which almost always involves allelic variants of a single HLA gene locus.

Defense mechanisms

Typically, potentially pathological autoimmune reactions can be prevented by mechanisms of immunological tolerance, clonal silencing, and clonal anergy. Any autoreactive lymphocytes that are not controlled by the above mechanisms are usually maintained by Foxp3-positive regulatory T cells. A defect in regulatory T cells can lead to the failure of one of the defense mechanisms,

resulting in an autoimmune condition. Anti-idiotypic antibodies (antibodies to the antigen-binding site of other antibodies) can interfere with the regulatory activity of antibodies.

Discussions

Drug hypersensitivity is an immune-mediated reaction. Symptoms range from mild to severe and include skin rash, anaphylaxis, and serum sickness. Diagnosis is made clinically; skin tests are informative. Treatment includes discontinuation of the drug, antihistamines (as indicated), and sometimes desensitization.

Drug hypersensitivity is distinct from toxic and adverse effects that may arise from the drug itself, as well as from problems related to drug interactions.

Pathophysiology of drug hypersensitivity

Some proteins and many polypeptide drugs (e.g., insulin, therapeutic antibodies) can directly stimulate antibody production. However, many drugs act as haptens, covalently binding to serum or cellular proteins, including proteins that make up the major histocompatibility complex (MHC) molecules. This binding makes the protein-drug complex immunogenic, stimulating antibody production and/or a T-cell response to the drug. Haptens can directly bind to MHC class II molecules, directly activating T lymphocytes. Some drugs act as prohaptens. Prohaptens are converted to haptens through metabolic reactions; for example, penicillin itself is not an antigen, but its major breakdown product, benzylpenicilloic acid, can combine with tissue proteins to form benzylpenicilloyl (BPO), the major antigenic determinant. Some drugs bind directly to and stimulate T cell receptors (TCRs); the clinical significance of nonhapten binding to the TCR remains to be determined (1).

It is not clear how primary sensitization occurs and how the innate immune system is initially involved, but once a drug has stimulated an immune response, cross-reactivity to drugs within and between classes is observed. For example, patients who are sensitive to penicillin are more likely to react to semisynthetic penicillins (e.g., amoxicillin, carbenicillin, ticarcillin). In previous studies, approximately 10% of patients with unknown etiology of penicillin sensitivity reacted to cephalosporins with a similar beta-lactam structure; this data has been cited as evidence of cross-reactivity between these drug classes. However, in more sophisticated studies (2), only approximately 2% of patients with penicillin allergy, as determined by skin testing, reacted to cephalosporins; approximately the same percentage of patients responded to structurally unrelated antibiotics (e.g., sulfa drugs). Some specific interactions (e.g., between sulfonamide antibiotics and non-antibiotics) are associated with a predisposition to allergic reactions rather than specific immune interactions.

Research results:

The signs and symptoms of drug allergies vary from patient to patient and from drug to drug, and the same drug can cause different reactions in different patients. The most serious manifestation is anaphylaxis (type I hypersensitivity reaction); Exanthema (such as a measles-like rash), urticaria, and fever are common. Persistent drug reactions—repeated reactions in the same part of the body each time you take the same drug—are rare.

Some specific clinical syndromes may involve other types of hypersensitivity reactions in the pathological process:

a. Serum sickness

b. Drug-induced immune hemolytic anemia

c. DRESS syndrome (drug rash with eosinophilia and systemic symptoms)

d. Respiratory symptoms

e. Kidney symptoms

f. Other autoimmune events

Serum sickness usually begins 7 to 10 days after exposure to serum and is characterized by fever, arthralgia, and rash. The mechanism of this disease is a type III hypersensitivity reaction, which is caused by the formation of drug-antibody complexes and the activation of components of the complement system. Some patients develop severe arthritis, edema, or gastrointestinal symptoms. Symptoms resolve spontaneously and last 1 to 2 weeks. Beta-lactam and sulfonamide antibiotics, iron dextran, and carbamazepine are the most common causes of this condition.

Drug-induced immune hemolytic anemia can develop when there is an antibody-drug-erythrocyte interaction (e.g., with cephalosporins or cefotetan) or when the drug (e.g., fludarabine, methyldopa) has a specific effect on the erythrocyte membrane, which triggers the production of autoantibodies. These reactions are classified as type II hypersensitivity reactions.

DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) or drug hypersensitivity syndrome (DHS) is a type IV hypersensitivity reaction that can develop within 12 weeks of starting drug therapy and can be exacerbated by dose escalation. Symptoms may persist or recur for several weeks after drug discontinuation. Patients present with eosinophilia and often develop hepatitis, exanthema, facial edema, generalized edema, and enlarged lymph nodes. Carbamazepine, phenytoin, allopurinol, and lamotrigine are the most common agents that cause this condition.

Pulmonary reactions may occur with certain drugs (e.g., bleomycin, amiodarone, nitrofurantoin, amphotericin B, sulfonamides, sulfasalazine). These drugs can cause respiratory symptoms (as opposed to wheezing seen in type 1 hypersensitivity reactions), deterioration of lung function, and other pulmonary changes (drug-induced lung injury, often interstitial lung disease). These effects are believed to be primarily types III and IV hypersensitivity reactions.

The most common allergic reaction involving the kidneys is tubulointerstitial nephritis; it is usually caused by nonsteroidal anti-inflammatory drugs (NSAIDs, including COX-2 inhibitors, methicillin, antimicrobials, and cimetidine). Type I, III, and/or IV hypersensitivity reactions may occur.

Other autoimmune phenomena may also occur. Hydralazine (not registered in the Russian Federation), propylthiouracil, and procainamide can cause a systemic lupus erythematosus (SLE)-like syndrome, which is a type III hypersensitivity reaction. The syndrome can be mild (with arthralgia, fever, and rash) or severe (with serositis, high fever, and severe malaise), but usually does not affect the kidneys or central nervous system. Antinuclear antibody testing is positive. Penicillamine can cause SLE and other autoimmune diseases (e.g., myasthenia gravis, which is a type II hypersensitivity reaction). Certain drugs, including antithyroid drugs, antituberculosis drugs, some antibiotics, allopurinol, hydralazine, and atorvastatin, can cause vasculitis associated with perinuclear antineutrophil cytoplasmic autoantibodies (pANCA). p-ANCA autoantibodies are directed against myeloperoxidase (MPO) and induce type II hypersensitivity reactions. Immune checkpoint inhibitors, which are widely used for cancer immunotherapy, can cause immune-mediated adverse reactions. These effects result from nonspecific activation of the immune system and can affect almost any organ system; however, they most commonly affect the skin, liver, gastrointestinal tract, heart, and endocrine system.

Drug hypersensitivity is diagnosed when a reaction to a drug occurs within a short time: from a few minutes to a few hours after taking the drug. However, many patients experience late reactions of unknown origin. In some cases, when it is impossible to find an adequate substitute (for example, when penicillin is needed to treat syphilis), skin tests should be performed.

Skin tests

Type I (IgE-mediated) hypersensitivity tests are helpful in diagnosing reactions to beta-lactam antibiotics, foreign (xenogeneic) serum, and some vaccines and polypeptide hormones. However, only a small percentage of patients who report penicillin allergy have positive skin tests (1). In

addition, tests for many drugs (including cephalosporins) are not informative and, because they diagnose only IgE-mediated allergies, do not allow predicting the development of measles-like rash, hemolytic anemia, or nephritis.

If patients with a history of immediate hypersensitivity must receive penicillin, a penicillin skin test may be performed. BPO-polylysine conjugate and benzylpenicillin are used as controls with histamine and saline. A skin prick test is performed first. If the patient has a history of severe anaphylactic reactions, the reagents for the initial test should be diluted 100-fold. If the skin prick test result is negative, intradermal tests may be performed. If the skin test results are positive, patients should be prescribed penicillin only as part of a drug desensitization protocol. If the test results are negative, a serious reaction is highly unlikely, but not impossible. Thus, after a negative skin test result, an oral amoxicillin challenge is often performed to completely exclude the possibility of an IgE-mediated allergy.

For skin testing for xenogeneic serum, patients without a history of atopy and who have not previously received xenogeneic (e.g., horse) serum preparations are first tested with a prick test using a 1:10 dilution; if the test result is negative, 0.02 ml of a 1:1000 dilution is administered intradermally. In susceptible patients, a blister larger than 0.5 cm in diameter is formed within 15 minutes. Initially, all patients who may have previously received serum preparations - regardless of their reaction - or who are suspected of having a history of allergy, the 1st prick test is performed at a 1:1000 dilution; if the result is negative - at a 1:100 dilution, and if the result is negative again, then a 1:10 dilution is used as a cutoff. Negative results exclude the possibility of anaphylaxis, but do not predict the occurrence of serum sickness in the future.

Other types of research

Drug challenge tests involve administering drugs that can cause hypersensitivity reactions in increasing doses until a reaction occurs. Such testing appears to be safe and effective when performed under controlled conditions.

Because drug hypersensitivity is associated with certain leukocyte class I haplotypes, genotyping patients from certain ethnic groups may help identify those at increased risk of hypersensitivity reactions (2).

Conclusion

Tests for hematologic drug reactions include direct and indirect antiglobulin tests. Tests for drugs that cause other types of hypersensitivity (e.g., allergen-specific serum IgE testing, histamine release, mast cell or basophil degranulation, lymphocyte transformation) are unreliable or experimental.

Cases such as drug fever, non-itchy skin rashes, and mild reactions from other organs and systems do not require any treatment other than discontinuation of the drug (see other chapters of the Manual for treatment of specific clinical reactions).

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