

Basic Concepts and Definitions of Alergology

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Abstract

The future of medicine belongs to immunology and alergology. I tried to not be too wide in description, but on the other hand to mention the most important concepts of alergology to make access to these diseases more understandable, logical and more useful for our patients, that without complex pathophysiology and mechanism of immune reaction, we gain some basic insight into immunological principles. The name allergy to medicine was introduced by Pirquet in 1906, and is of Greek origin (allos-other + ergon-act; different reaction), essentially representing the reaction of an organism to a substance that has already been in contact with it, and manifested as a specific response that manifests as either a heightened reaction, a hypersensitivity, or as a reduced reaction immunity. Synonyms for hypersensitivity are: altered reactivity, reaction, hypersensitivity. The word sensitization comes from the Latin (sensibilitas, atis, f.), which means sensibility, sensitivity, and has retained that meaning in medical vocabulary, while in immunology and allergology this term implies the creation of hypersensitivity to an antigen. Antigen comes from the Greek words, anti-anti + genos-genus, the opposite, anti-substance substance that causes the body to produce antibodies.

Keywords

Hypersensitivity; IgE,antibodies; Allergology; Immunology; Antigens; Atopia; Immunoglobulin; Antihistamines

Introduction

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Allergy

Allergic disease is a complex of symptoms and signs in which immune mechanisms play a crucial role, and is basically most mediated and triggered by antibodies, the antigen-antibody response, and is always accompanied by noticeable clinical symptomatology. The most common antibodies involved in allergic events are IgE classes. Allergens are antigens that cause an allergic reaction. Hypersensitivity is the onset of objectively reproducible symptoms or signs that are caused by exposure to a defined stimulus at a dose tolerant of a normal person. Atopia is a Latinized word (atopicus, a, um) from the Greek a- private, i.e. which excludes the + topos- place, which means the one not in the right place. Atopy is a personal and/or familial preference, sensitivity, and generation of immunoglobulin class E (IgE antibodies) antibodies in response to common allergen exposure, usually protein, more common in childhood and adolescence. As a consequence, such individuals may develop typical symptoms of asthma, rhino conjunctivitis or eczema. The term atopy is reserved for the genetic predisposition to IgE sensitization to allergens that are commonly found in the environment and with which everyone comes in contact, but which most people do not produce, for a long time, IgE antibody-mediated response. Atopy is actually the clinical definition for a strong response of sensitized persons mediated by IgE antibodies. The term atopy cannot be used without evidence of IgE sensitization, either by finding serum IgE antibodies and or by a positive skin prick test. In other words, the continuous and abundant production of immunoglobulin E on environmental antigens is a key process underlying atopy [1-3, 21].

Hypersensitivity

The immune system protects the body from infection. This is achieved by synergizing the specific and nonspecific immune system. However, the immune response in itself can cause tissue damage and disease. Pathologic immune responses or those that cause damage are called hypersensitivity reactions. The name originated from the idea that an immune response to an antigen can lead to sensitivity to exposure to that antigen and therefore hypersensitivity indicates an over- or inappropriate immune response. Hypersensitivity reactions can occur in two cases. First, the immune response to foreign antigens can be disrupted or uncontrolled, causing tissue damage. Second, the immune response may be directed toward its own (autologous) antigens, as a result of interruption of auto tolerance. The response to its own

antigens is called autoimmunity, and the disorders caused by this response are called autoimmune diseases [1-5].

Types of hypersensitivity reactions

1. An allergic reaction can only be considered a reaction in which:
2. Determine the causal link between contact with the antigen and the occurrence of the damage
3. Identify the immune mechanism causing the damage.

Hypersensitivity reactions are usually classified on the basis of major immune mechanisms responsible for tissue damage and disease, most commonly according to Coombs and Gell since 1975 into four basic types:

Type I: Anaphylactic or reagent dependent reactions; early hypersensitivity caused by the release of mediators from mast cells. It is most commonly triggered by the production of environmental IgE antibodies and the binding of IgE antibodies to mast cells in different tissues.

Type II: Antibody-dependent cytotoxic (or stimulating) responses Non-IgE antibodies can cause the disease in two ways. Antibodies directed against cell and tissue antigens can damage these cells or tissues or disrupt their functions. These diseases are said to be caused by antibodies and are type II hypersensitivity.

Type III: Hypersensitivity reactions caused by immune complexes. Sometimes, antibodies against soluble antigens can form complexes with antigens, and these immune complexes can precipitate in the blood vessels of different tissues and cause inflammation and tissue damage. These diseases are called immune complex diseases and are type II hypersensitivity.

Type IV: late or cell-mediated hyper sensitivity. Some diseases result from T-lymphocyte reactions, often against their own antigens in the tissues. These T-cell diseases represent type IV hypersensitivity. This classification is based on initial events when an antigen and antibody or antigen and sensitizing cell reaction occurs, and such pure reactions are found on experimental occasions. However, allergic reactions in clinical practice involve secondary events with different immune mechanisms such that those reactions most commonly in the development of the disease become reactions of two or more types of hypersensitivity. In most patients, allergies are mediated by IgE antibodies, and those that are not, are triggered by various primary immune mechanisms, e.g. G-class (IgG) immunoglobulins, immune complexes and cells [1,4,21,22].

Early Hypersensitivity

It represents a rapid response of blood vessels and smooth muscle mediated by IgE antibodies and mast cells, often accompanied by inflammation. IgE mediated allergies usually have a biphasic nature, after an early or immediate reaction, a late or delayed reaction occurs after three to six hours, characterized by involvement in cell inflammation. A delayed

reaction is also characterized by prolonged hyper reactivity, which in the case of prolonged exposure, leads to structural and functional changes that are further the cause of the characteristic symptomatology of the disease. An early hypersensitivity reaction can affect different tissues and vary in intensity in different individuals.

The atopic clinical syndromes of early hypersensitivity, acute and chronic include:

1. Allergic bronchial asthma (seasonal and perennial)
2. Allergic rhinitis (seasonal and perennial)
3. Allergic conjunctivitis (seasonal)
4. Atopic dermatitis
5. Allergic bronchopulmonary aspergillosis

Type I allergic reactions independent of atopic constitution (acute):

1. IgE mediated drug reactions
2. IgE mediated nutritional allergy
3. IgE-mediated responses to insect veins

These reactions are most commonly clinically manifested as:

1. Acute urticaria;
2. Acute angioedema
3. Anaphylaxis
4. A sudden asthmatic attack

Allergic diseases are clinically manifested as rhinitis, asthma, conjunctivitis, urticaria, gastrointestinal allergy, atopic eczema, allergic contact dermatitis and sometimes as life-threatening anaphylaxis [1,2,19-22]. Allergic rhinitis is clinically defined as a symptomatic nose disorder, most commonly caused by inflammation-mediated IgE antibodies after exposure of the nasal mucosa to an allergen. If the symptoms are seasonal, e.g. pollen-induced allergic rhinitis, the appropriate name would be seasonal allergic rhinitis. When allergy mediated by IgE to antibodies manifests with eye symptoms, we call it allergic conjunctivitis, usually associated with allergic rhinitis, in which case we call this condition allergic rhino conjunctivitis. In addition to IgE-mediated conjunctivitis, allergic disease is also contact allergic conjunctivitis which involves Th1 lymphocyte-mediated allergy. Polynosis or pollenosis, also called pollen fever, allergic rhinitis, sinusitis, conjunctivitis, and in some patients is associated with bronchial asthma. Asthma is a chronic inflammation that occurs in the airways when exposed to various factors. Chronically inflamed airways are hypersensitive, become narrowed, and airflow is restricted (bronchospasm, mucus plugs, and inflammation progression) when exposed to different airway risk factors. In most cases, asthma is triggered by an IgE antibody, and the right term for that asthma would be IgE mediated allergic asthma. Dermatitis is a local inflammation of the skin. Eczema is a proposed term that replaces the earlier term "atopic eczema/dermatitis syndrome" [1,5-8,11]. Atopic eczema is inflammation of the skin in children and young people with atopic

constitution, mediated by IgE antibodies, in which the underlying disease is a genetic predisposition for the sensitivity of the target organ. Allergic urticaria is an inflammatory reaction mediated by immune mechanisms, usually mediated by IgE antibodies, although it may also be associated with the formation of immune complexes. Allergic contact urticaria is one that develops locally at the site of contact with the allergen and is mediated by IgE antibodies, e.g. allergy to the hands of people allergic to latex wearing rubber gloves or urticaria on the legs of atopic sensitized to grass pollen after walking in the meadow. Food allergy is an appropriate expression when immune mechanisms are proven. If IgE antibodies are involved in the reaction, then a responsive, IgE-mediated food allergy is appropriate. Drug allergy is a reaction when immune mechanisms have been demonstrated, mediated by antibodies or cells. The reaction may be immediate (early) or delayed (late), suggesting a likely immune mechanism, that is, mediated by IgE antibodies or cells. Allergy to insect sting or insect bite is an occurrence of insensitivity to insect venom and saliva mediated by immune mechanisms. When IgE antibodies are involved in the hypersensitivity reaction, then it is emphasized that it is IgE mediated allergy to insect venom or saliva. Anaphylaxis is a general hypersensitivity reaction to a life-threatening organism. The term allergic anaphylaxis is used when the reaction is mediated by immune mechanisms. If the anaphylactic reaction were mediated by IgE antibodies, it is called IgE mediated allergic anaphylaxis [1-8].

Allergens

Antigens that induce early hypersensitivity reaction, In order for a person with a predisposition to an allergy to become allergic, prior contact with the antigen, in this case the allergen, to which the immune response develops sensitization is necessary, after which repeated contact and with a small amount of the same allergen leads to a manifest allergic reaction or hypersensitivity. It follows that avoidance allergen contact should be an integral part of the therapeutic and preventative care of symptomatic patients in the prevention of exacerbation of the disease. There is a wide range of antigen-allergens that can be divided into the following for practical reasons:

1. Aeroallergens
2. Insect bites
3. Food allergens
4. Contact allergens
5. Medicines
6. Professional allergens

Diagnosis is based on:

1. Clinical picture
2. Prick tests for inhalation, medicaments and venom insects
3. Detection of allergen-specific IgE antibodies - medications, nutritional allergens
4. Determination of eosinophils: blood, BAL, induced sputum
5. Determination of mediators (ECP, tryptase, etc.)

Provocative tests

Respiratory allergies generally include allergic rhinitis and asthma. Apart from the characteristic symptomatology or clinical picture, the diagnosis of these diseases must also take into account the place of residence, environment, work, living conditions, time, season of occurrence, for which a targeted history is taken. With anamnesis and clinical presentation, skin allergy tests have been of paramount importance for decades in assessing a patient's allergic status. Since the beginnings of allergology, skin tests have been used in tests. First, until the 80's. XX. The intradermal test has been used for centuries, and for the last 25 years, in the world and in our country, it has been generally accepted by skin prick test (SPT) or prick test. This test is more specific than intradermal, it is not risky, it better correlates with broncho provocative tests, it is less painful and less expensive. The cutaneous intradermal test is more sensitive and is reserved for allergens negative for SPT, and for testing hypersensitivity to drugs and insects, where anaphylactic reactions may occur even at very low titres of specific IgE. In addition to skin allergy tests, in vivo nasal and broncho provocative specific and nonspecific tests are used to diagnose. In vitro treatment of patients for the diagnosis of allergy is also important in vitro tests, determination of total and specific IgE, the number of eosinophils in the blood, coughing and nasal swab. Exposure tests and analysis of harmful environmental factors are less commonly used in the diagnosis of airway allergies, for example in occupational respiratory diseases. In addition to the above treatment related to type I reactions, type II, type II and type IV reactions in the airways also occur by Coombs and Gell, which cause other diseases, vasculitis, extrinsic allergic alveolitis, granulomas, and require additional immune treatment.

Skin prick test

Today, most allergy dispensaries, even in our country, use a skin allergy test with a lancet, SPT. It is a semi-quantitative method for the detection of in vivo specific IgE antibodies, that is, sensitized persons. It is very responsive, specific, fast, reproducible, inexpensive, slightly painful and does not require expensive technology. The test is safe and there are almost no adverse reactions. Standardized allergen preparations and methods, recommended by WHO (World Health Organization) and EAACI (European Academy of Allergology and Clinical Immunology) with allergens characteristic of the geographical area of the population where testing is performed, are used. Several papers have demonstrated the high specificity of this test in the assessment of sensitization, that is, atopy, and some published papers in the assessment of sensitization rely only on SPT. Skin allergy testing, SPT is performed by stabbing the skin of the volar side of the forearm with a drop of allergen applied solution. The sterile lancet is used once for each allergen, has a tip of 1 mm in length with a stop which prevents it from penetrating deeper into the skin, When performing a skin test, it is necessary to make a negative and positive control with allergen testing and comparison of findings. Negative control is performed with saline to check for nonspecific histamine liberation resulting from e.g. due to physical skin trauma or demographics. Positive control is usually performed with a histamine solution of a concentration of 1 mg/ml to check the norm

reactivity of the skin. Minutes after skin testing, redness, itching, burning and induration occur at the injection site through a drop of histamine solution and, at sensitized on allergenic sites, to which they are hypersensitive. First, on the volar side of the forearm, the places for applying the droplets of the fluid to be tested are indicated. The epidermis of the skin is penetrated through the droplets with the tip of the lancet at an angle of 90°, whereby no bleeding can occur with a properly performed test. The test is read after 15-20 minutes from the performance, it should be emphasized that the histamine reaction occurs earlier and disappears sooner than allergic ones. A significant positive reaction is considered to be induration with a mean diameter of 3 mm and more and redness of 10 mm and more. Of course, the negative and positive control reaction must be taken into account. Namely, the reaction to an allergen is not positive, if the finding of induration is not greater than the negative control and is not equal to or greater than the positive control. The test is not performed on the skin where there would be changes in active eczema, at the site of topical administration of corticosteroids or immunomodulatory fats. Chromo lines and antihistamines should be omitted for at least three days from therapy. In a small number of atopic patients at the site of an early skin reaction, late or delayed reactions may occur in the form of induration, erythema and itching. These reactions are usually longer than early and last for 3-24 hours. It should be borne in mind that in skin allergy testing patients have significant variations in skin reactivity that do not have to match the severity of the disease symptoms. You should also take into account that a positive reaction does not mean an allergic disease, as well as a negative finding does not exclude. Clinical indications for repeated testing are: a change in disease symptoms, b exposure to new allergens, inconsistency with finding specific IgE, and c assessment of evaluation of the effect of specific immunotherapy after 3-5 years of treatment [1-9].

Serum IgE determination

There are no atopic diseases without IgE antibodies. Clinically manifest disease occurs with allergic reactions that occur after the binding of antigens (allergens) to IgE found on basophils and mast cells, where biologically active amines, primarily histamine and serotonin, are secreted from these cells. Therefore, the determination of total and specific IgE in serum is essential in allergic diagnostics. There are several in vitro methods for determining total and specific IgE. The basic principle of these tests is based on the high specificity of the antigen-antibody reaction. The high sensitivity and use of different markers allow the detection and quantification of very small amounts of single analytes (eg, IgE) and from a small amount of serum. As markers and in various immune tests, isotopes, enzymes, chemiluminescent molecules, free radicals, etc. Depending on the marker, detection methods were named.

Total IgE

The concentration of total IgE in the umbilical cord is about 1 nanogram / mL, in children it reaches the “normal value” at puberty and is maintained throughout the life of the expected value up to 200 nanograms / mL in healthy persons, and in allergic persons they are often

much higher (reference values are stated and can be different for different labs). Findings in reference ranges do not rule out allergy, as do elevated IgE values they often do not mean allergies due to other influences, primarily parasitic infections.

They are most commonly used to determine total IgE:

- Radio immunosorbent assay (RIST - Radio Immuno Sorbent assay,
- Fluoro immunoassay (FIA-Fluoro Immunoassay,
- Fluoroenzyme immunoassay (FEIA-CAP System, Fluoro Enzyme Immuno Assay)

Specific IgE

Elevated serum IgE levels suggest a possible atopic etiology. However, detection of a specific IgE antibody and its quantification is required to confirm the diagnosis. Also, when the findings of an allergic treatment after SPT are dubious, or we want to confirm those findings in further processing, specific IgE is determined. Serum specific IgE determination should be performed by a proven technique and can be applied at any age. The quantitative specific test has high real validity; the positive test shows the presence of IgE specific for the allergen tested. Specificity and sensitivity range from 85-95%. Specific IgE detects sensitization to a suspected allergen and is a helpful aid in diagnosis, since only people who are sensitized to an allergen can develop an allergic disease [1-3].

Therapy of the allergic group of early hypersensitivity

Early hypersensitivity response therapy is aimed at inhibiting mast cell degranulation, antagonizing the effect of mast cell mediators and reducing inflammation. First of all, it is recommended to avoid allergens. Usually antihistamines are used to treat pollen sneezing, medicines that relax bronchial smooth muscle for asthma and adrenaline for anaphylaxis. In diseases in which the pathogenesis of inflammation is an important component, such as asthma, corticosteroids are used to inhibit inflammation. Many patients are favorably affected by repeated administration of low doses of allergens, called desensitization. Such treatment may be effected by altering T cell responses, preventing the dominance of Th2 responses, or inducing tolerance (energy) of allergen-specific T cells, that is, allergen-specific immunotherapy for type I responses to insect veins, allergic rhinitis and bronchial asthma in remission. It is important to ask why evolution has preserved the immune response mediated by IgE antibodies and mast cells whose main effects are pathological. There is no good answer for this puzzle. IgE antibodies and eosinophils are known to be an important defense mechanism in helminth infections and mast cells play a role in innate immunity against some bacteria, but it is unknown why common environmental antigens trigger Th2 cell and mast cell responses that can cause significant damage.

Type II: antibody-dependent cytotoxic (or stimulating) responses

Occurs when antibodies other than IgE class (IgG or IgM) react with antigenic components in cells or on their surfaces, thereby forming immune complexes that precipitate in blood vessels.

Diseases in which type II hypersensitivity is of primary importance:

- Autoimmune hemolytic anemia
- Acute rheumatic fever
- Autoimmune thrombocytopenia
- Autoimmune leukopenia
- Hashimoto thyroiditis
- Graves' disease
- Pernicose anemia
- Myasthenia gravis
- Good pasture syndrome
- Hyper acute allograft rejection
- Pemphigus, pemphigoid

The two diseases that are best described are rare, late sequelae of streptococcal infections. Following these infections, individuals create antistreptococcal antibodies that cross-react with cardiac muscle antigens. The deposition of these antigens in the heart triggers an inflammatory disease called rheumatic fever. Others may produce antistreptococcal antibodies that precipitate in the kidney glomeruli, causing post-streptococcal glomerulonephritis.

Diagnostics

- Clinical imaging
- Laboratory tests
- (KKS; biochemical analyzes, hormone concentrations)
- Autoantibody detection
- Functional testing

Coombs test (detection of anti-erythrocyte antibodies); Ant microsomal antibodies and anti-thyroglobulin antibodies: Autoimmune thyroiditis, Hashimoto thyroiditis, anti TPO 80-90%, anti TG 60-90%, postpartum thyroiditis, anti TPO 90%; Graves' disease, anti TPO and TG 50-70% (1, 12-18).

Treatment of diseases in which pathogenesis is II type of hypersensitivity

- Antigen elimination
- Immunosuppressive therapy: corticosteroids, azathioprine, mycophenolate mofetil
- IV Ig immunomodulatory therapy

Diseases in which type III hypersensitivity is of primary importance

- Serum disease
- Systemic lupus erythema
- Rheumatoid arthritis
- Cryoglobulinemic vasculitis
- Hypersensitive vasculitis (medicines, infections)
- Nodose polyarthritis
- Post-streptococcal glomerulonephritis
- Glomerulonephritis in sepsis
- Hypersensitive pneumonitis

Diagnostics

- Clinical picture
- Detection of circulating antibodies (IIF, ELISA, blot, agglutination);
- Concentration of complement components C3, C4
- Detection of circulating immune complexes
- Detection of Deposited Immune Complexes (DIFs)
- Path histological findings

Treatment of diseases in which pathogenesis is III type of hypersensitivity

- Antigen elimination (serum disease)
- Application of specific antimicrobial therapy (sepsis, infection)
- Non-steroidal anti-inflammatory drugs (COX1 and 2)
- Immunosuppressive therapy: corticosteroids, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, chloroquine, leflunomide
- Immunomodulatory therapy (IVIg, anti TNF-alpha At, IL-1 R antagonist)
- Diseases in which type IV hypersensitivity is of primary importance
- Contact allergic dermatitis
- Granulomatic diseases (sarcoidosis, foreign body reaction)
- Response to intracellular pathogens (mycobacterium TB, listeria, candida)
- Allograft rejection

Therapy of type IV hypersensitivity

- Antimicrobial therapy
- Elimination of allergens
- Elimination of a foreign body
- Discontinuation of medication
- Immunosuppressive therapy

Table1: A combination of multiple types of hypersensitivity

Autoimmune disease	II	III	IV
Diabetes mellitus type I	X		X
Acute Transplant Rejection	X		X
Pernicious Anemia	X		X
Hashimoto Thyroiditis	X		X
SLE (lupus)	X	X	
Rheumatoid Arthritis		X	X
Hypersensitivity Pneumonitis		X	X

Epicutaneous (patch) test

The epicutaneous or patch test is performed using a patch method using standard series allergens or targeted professional allergens. Allergens are applied on the back skin in the interscapulum region or on the volar side of the forearm. In a non-toxic and prescribed (by European standards) allergen, the allergen is applied to a healthy, pre-cleaned skin (gasoline, etheromyl alcohol). 0.02-0.03 g of allergen in petroleum jelly or other medium - solvent - is placed on filter paper of 1 / 1cm in case of professional allergens. The cloth is covered with cellophane coating 2x2 cm and covered with leukoplasty 5x5 cm. Since this is IV. the type of reaction by Coombs and Gell, the late type hypersensitivity reaction, the allergen comes into contact with the patient's skin, and the reaction is read after 48,72 and 96 hours. Ready-made, commercial test strips from different manufacturers can also be used, e.g. Beiersdorf, Finn Chambre and Lohman. This test is the gold standard in the diagnosis of contact allergic dermatitis and is also performed for all types of late dermatitis. The standard batch usually contains 26 allergens. These are allergens from everyday life and work, such as chromium, nickel, cobalt, mercury ursol, formaldehyde, epoxy resins, charcoal tar, peruvian balm, mercapto compounds, tiuram compounds, paraben mixture, thimerosal, primine and more. Allergens are used for targeted testing by profession. If the patient is on sick leave for a longer period, the test does not need to be performed. The most common allergens are turpentine oil, coal tar, building materials - cement, lime, sand and iron - and pesticides. Allergens are made from samples from a workplace that are suspected to be the source of the allergy. There is a range of allergens in the European offering for various occupations [1,13,17-22].

Table2: The criteria for reading the epi cutaneous test.

Type of skin reaction	Test reading
irritant	IR (red within 30 minutes)
Negative	0 (no reaction)
Positive	Positive + (slight erythema and edema with redness) off-site reaction) + + + (numerous papules and vesicles, by which bulla, eroded surface and very moist)

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