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Hypersensitivity Reactions, Immediate

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Introduction

Hypersensitivity reactions (HR) are immune responses that are exaggerated or inappropriate against an antigen or allergen. Coombs and Gell classified hypersensitivity reactions into four forms. Type I, type II, and type III hypersensitivity reactions are known as immediate hypersensitivity reactions (IHR) because occur within 24 hours. Antibodies including IgE, IgM, and IgG mediate them.

Type I or Anaphylactic Response

Anaphylactic Response is mediated by IgE antibodies that are produced by the immune system in response to environmental proteins (allergens) such as pollens, animal danders or dust mites. These antibodies (IgE) bind to mast cells and basophils, which contain histamine granules that are released in the reaction and cause inflammation. Type I hypersensitivity reactions can be seen in bronchial asthma, allergic rhinitis, allergic dermatitis, food allergy, allergic conjunctivitis, and anaphylactic shock.

Anaphylaxis

Anaphylaxis is a medical emergency because can lead to an acute, life-threatening respiratory failure. It is an IgE-mediated process. It is the most severe form of an allergic reaction, where mast cells suddenly release a large amount of histamine and later on leukotrienes. In severe cases intense bronchospasm, laryngeal edema, cyanosis, hypotension, and shock are present.

Allergic bronchial asthma

Allergic bronchial asthma is an atopic disease, characterized by bronchospasm. It may also be a chronic inflammatory disease. In its etiology, and environmental factors along with a genetic background play an important role. The diagnosis is dependent on history and examination. In allergic bronchial asthma, IgE is elevated, and sputum eosinophilia is common. Epidemiologically, a positive skin prick test or specific IgE are risk factors for asthma.

Allergic rhinitis

Allergic rhinitis is another atopic disease where histamine and leukotrienes are responsible for rhinorrhea, sneezing and nasal obstruction. Allergens are similar to those found in bronchial asthma. Nasal polyps may be seen in chronic rhinitis.

Allergic conjunctivitis

Allergic conjunctivitis presents with rhinitis and is IgE-mediated. Itching and eye problems including watering, redness, and swelling always occur.

Food allergy

One must differentiate food allergy (IgE-mediated) from food intolerance that can be cause for a variety of etiology including malabsorption and celiac disease. It is more frequent in children as seen in cow's milk allergy. Food allergy symptoms mostly affect the respiratory tract, the skin, and the gut. Skin prick tests are helpful to test for food allergens that can trigger severe reactions, e.g., peanuts, eggs, fish, and milk.

Atopic eczema

Atopic eczema is an IgE-mediated disease that affects the skin and has an immunopathogenesis very similar to that of allergic asthma and allergic rhinitis, which are present in more than half of the diseased. Radioallergosorbent (RAST) may reveal the specificity of the IgE antibody involved but has little help in management.

Drug allergy

Drugs may cause allergic reactions by any mechanism of hypersensitivity. For example, penicillin may cause anaphylaxis, which is IgE-mediated but must responses be trivial. Penicillin cross-reacts with other semisynthetic penicillins including monobactams and carbapenems and may also cross-react with other antibiotics such as cephalosporins.

Type II or Cytotoxic-Mediated Response

IgG and IgM mediate cytotoxic-mediated response against cell surface and extracellular matrix proteins. The immunoglobulins involved in this type of reaction damages cells by activating the complement system or by phagocytosis. Type II hypersensitivity reactions can be seen in immune thrombocytopenia, autoimmune hemolytic anemia, and autoimmune neutropenia.

Immune thrombocytopenia (ITP)

ITP is an autoimmune disorder that occurs at any age. Phagocytes destroy sensitized platelets in the peripheral blood. Clinically, it manifests by thrombocytopenia with shortened platelet survival and increased marrow megakaryocytes. Sudden onset of petechiae and bleeding from the gums, nose, bowel, and urinary tract occurs. Bleeding can accompany infections, drug reactions, malignancy and other autoimmune disorders such as thyroid disease and SLE.

Autoimmune hemolytic anemia (AIHA)

There are two types of immune hemolytic anemia: IgG-mediated (warm AIHA) and IgM-mediated (cold AIHA). The warm type may be idiopathic autoimmune or secondary to other diseases such as malignancy affecting the lymphoid tissues. The cold type may be idiopathic or secondary to infections such as Epstein-Barr virus. The primary clinical sign of the two is jaundice. The laboratory diagnosis is made by a positive Coombs test, which identifies immunoglobulins and C3 on red blood cells.

Autoimmune neutropenia

Autoimmune neutropenia may be present with bacterial and fungal infections, or it may occur alone or with autoimmune diseases (SLE, RA, autoimmune hepatitis), infections and lymphoma. Bone marrow examination is needed if neutropenia is severe. For associated autoimmune disorders, an autoimmune antibody panel is necessary (ANA, ENA, and dsDNA).

Hemolytic disease of the fetus and the newborn (erythroblastosis fetalis)

The maternal immune system suffers an initial sensitization to the fetal Rh+ red blood cells during birth, when the placenta tears away. The first child escapes disease but the mother, now sensitized, will be capable of causing a hemolytic reaction against a second Rh+ fetus, which develops anemia and jaundice once the maternal IgG crosses the placenta.

Myasthenia gravis

Myasthenia gravis is an autoimmune disorder caused by antibodies to post-synaptic acetylcholine receptors that interfere with the neuromuscular transmission. It is characterized by extreme muscular fatigue, double vision, bilateral ptosis, deconjugate eye movements, difficulty swallowing, and weakness in upper arms. Babies born to myasthenic mothers can have transient muscle weakness due to pathogenic IgG antibodies that cross the placenta.

Goodpasture syndrome

Goodpasture syndrome is a type II hypersensitivity reaction characterized by the presence of nephritis in association with lung hemorrhage. In most patients, it is caused by cross-reactive autoantigens that are present in the basement membranes of the lung and kidney. A number of patients with this problem exhibit antibodies to collagen type IV, which is an important component of basement membranes.

Pemphigus

Pemphigus causes a severe blistering disease that affects the skin and mucous membranes. The sera of patients with pemphigus have antibodies against desmoglein-1 and desmoglein-3, which are components of desmosomes, which form junctions between epidermal cells. Pemphigus is strongly linked to HLA-DR4 (DRB1*0402), which is a molecule that presents one of the autoantigens involved in the immunopathogenesis of this disease (desmoglein-3).

Type III or Immunocomplex Reactions

These are also mediated by IgM and IgG antibodies that react with soluble antigens forming antigen-antibody complexes. The complement system becomes activated and releases chemotactic agents that attract neutrophils and cause inflammation and tissue damage as seen in vasculitis and glomerulonephritis. Type III hypersensitivity reactions can classically be seen in serum sickness and Arthus reaction.

Serum sickness

Serum sickness can be induced with massive injections of foreign antigen. Circulating immune complexes infiltrate the blood vessel walls and tissues, causing an increased vascular permeability and leading to inflammatory processes such as vasculitis and arthritis. It was a complication of anti-serum prepared in animals to which some individuals produced antibodies to the foreign protein. It was also experienced in the treatment with antibiotics such as penicillin.

Arthus reaction

Arthus reaction is a local reaction seen when a small quantity of antigens is injected into the skin repeatedly until detectable levels of antibodies (IgG) are present. If the same antigen is inoculated, immune complexes develop at the mentioned local site and in the endothelium of small vessels. This reaction is characterized by the presence of marked edema and hemorrhage, depending on the administered dose of the foreign antigen.

Etiology

Multiple causes of IHR depend on the type of antigen or allergen that trigger this inappropriate immune reactivity. In type I hypersensitivity reactions, the allergens are proteins with a molecular weight ranging from 10 to 40 kDa. These include cats, dust mite, German cockroaches, grass, rats, fungi, plants, and drugs. They stimulate the IgE production. Bee and wasp venoms, tree nuts (e.g., almond, hazelnut, walnut, and cashew), eggs, milk, latex, antibiotics (e.g., cephalosporins), heterologous antisera, hormones (e.g., insulin) and others including shellfish and anesthetics can trigger anaphylaxis.

In type II hypersensitivity reactions, the antigens can be found in the membrane of erythrocytes (e.g., A, B, O, C, c, D, d, E, e, K, k, Fy, M, and N). In transfusion reactions, all blood groups are not equally antigenic, e.g., A or B evoke stronger hypersensitivity reactions in an incompatible recipient than other antigens such as Fy.

In type III hypersensitivity reactions, the persistence of antigen from chronic infection or autoimmune diseases can develop complex immune diseases, including vasculitis and glomerulonephritis. Penicillin as an antigen can produce any hypersensitivity reactions, e.g., anaphylactic shock, hemolytic anemia, and serum sickness.

Epidemiology

Hypersensitivity reactions are very common. Fifteen percent of the world population will be affected by any type of allergic reaction during their lives. In the second half of this century, allergic diseases have increased. The cause of the increase is unknown, but it may reflect lifestyle changes, decreased breastfeeding, and air pollution. The hygiene hypothesis proposes that since IgE is no longer needed to protect against parasites in the Western world, the IgE-mast cell axis

has evolved in type I hypersensitivity reaction.

European data estimate that 0.3% of the population will be troubled by anaphylaxis at some point in their lives. In addition, 1 out of 3000 inpatients in the United States experiences a severe allergic reaction every year. However, the prevalence of bronchial asthma was 1.5% in Korea. Fernández-Soto et al., 2018 reported that fungal infections could be as high as 50% in inner cities and constitute a risk factor predisposed to the development of allergic bronchial asthma. Worldwide epidemiological data of anaphylaxis are scanty and remain unavailable in many countries.

Pathophysiology

In type I hypersensitivity reactions after a previous sensitization, the immunoglobulin (Ig) E is produced and binds to Fc receptors on mast cells and basophils. On encountering the allergen, it triggered cross-linking of mast-cell cytophilic IgE, causing the activation of mast cells and their degranulation of mediators that cause an allergic reaction. The mediators that participate in this type of hypersensitivity reaction include histamine and lipid mediators such as PAF, LTC₄, and PGD₂ that cause a vascular leak, bronchoconstriction, inflammation, and intestinal hypermotility. Enzymes (e.g., tryptase causes tissue damage) and TNF causes inflammation. Eosinophils release cationic granule proteins, e.g., major basic protein (causes killing of host cells and parasites) and enzymes (e.g., eosinophil peroxidase, which participates in tissue remodeling).

In type II hypersensitivity reaction antibodies against basement membranes produce nephritis in Goodpasture's syndrome. Myasthenia gravis and Lambert-Eaton syndrome are caused by antibodies that reduce the amount of acetylcholine at motor endplates, and autoantibodies to an intercellular adhesion molecule cause pemphigus.

In type III hypersensitivity reactions immune-complex deposition (ICD) causes autoimmune diseases, which is often a complication. As the disease progresses a more accumulation of immune-complexes occurs, and when the body becomes overloaded the complexes are deposited in the tissues and cause inflammation as the mononuclear phagocytes, erythrocytes, and complement system fail to remove immune complexes from the blood.

Histopathology

Human basophils present multi-lobed nuclei and distinctive granules. They can be found in local tissues including the nose, lungs, skin or gut in response to allergic and immune responses. The two populations of mast cells are mucosal and connective tissue. They have morphological and pharmacological differences. The mucosal mast cells can associate with a parasitic infestation, and connective tissue mast cells are smaller and live shorter. Both contain histamine and serotonin in their granules. Skin biopsy of patients with allergic dermatitis shows inflammatory infiltrate with few eosinophils, but their degranulation in the skin demonstrated in the biopsy stained with antibodies against eosinophil major basic protein (MBP). In the nasal smear of a patient with acute bronchial asthma, an infiltrate consistent of eosinophils, and polymorphonuclear cells with a normal cytoplasm stained with hematoxylin and eosin were shown.

In type II hypersensitivity reactions, autoantibodies bind to desmosome involved in cell adhesion, and autoantibodies in diabetes mellitus bind to islet cells. They can be demonstrated in tissues by immunofluorescence. The method that uses fluorescent antibodies has also been used in type III hypersensitivity reactions to demonstrate the presence of immune complexes in the intima and media of the arterial wall, as well as IgG and C3 deposits in kidney, joints, arteries, and skin. In Goodpasture syndrome, the antibodies involved are IgG and have the capacity to fix complement. Necrosis of the glomerulus, with fibrin deposition, is a major feature of this syndrome.

History and Physical

In type I hypersensitivity reactions there is a history of atopy or a patient suffering from an allergic condition (e.g., bronchial asthma, allergic rhinitis, or food allergy). It may associate with recurrent infections caused by viruses and bacteria. For instance, bronchial asthma may link to recurrent bacterial pneumonia. Clinically allergic disorders may accompany by airways inflammation, wheezing attack, bronchial hyper-responsiveness, tachycardia, tachypnea, intense itching of the eyes and nose, sneezing, rhinorrhea, dermatitis, and gastrointestinal symptoms. Anaphylaxis, the most severe type of allergy, is clinically characterized by bronchospasm, angioedema, hypotension, loss of consciousness, generalized skin rash, nausea, vomiting, and abdominal cramps among other symptoms.

In type II hypersensitivity reactions, a patient may report multiple blood transfusions, rhesus incompatibility, and drug history. Clinically, it may manifest as autoimmunity, e.g., autoimmune hemolytic anemia (characterized by jaundice), immune thrombocytopenia (characterized by bleeding disorders), and other blood dyscrasia (autoimmune neutropenia). In this type of hypersensitivity, drugs may attach to red blood cells and stimulate the production of anti-red blood cell antibodies or anti-dsDNA antibody that causes drug-induced systemic lupus erythematosus (SLE).

Type III hypersensitivity reactions may manifest as immune complex-mediated diseases including glomerulonephritis, vasculitis, serositis, arthritis, and skin manifestations of autoimmunity such as malar rash, which is due to photosensitivity. The prevalence of serum sickness has decreased dramatically because animal anti-serum is rarely used to treat or prevent infectious diseases. General manifestations of disease including anorexia, loss of weight, and asthenia may report in IHR.

Evaluation

The evaluation of immediate hypersensitivity includes complete blood cell count, assessment of immunoglobulins, skin prick test, and detection of autoantibodies.

Quantitative Serum Immunoglobulins

- IgG (involved in Type II and III HR)
- IgM (involved in Type II and III HR)
- IgE (elevated in allergic diseases)

Total Leukocyte Count and Differential

- Hb (decreased in autoimmune hemolytic anemia)
- Neutrophils (decreased in autoimmune neutropenia)
- Lymphocytes (decreased in autoimmune lymphopenia)
- Platelets (decreased in immune thrombocytopenia)

Autoimmunity Studies

- Anti-nuclear antibodies (ANA, present in systemic autoimmune disorders, such as SLE and RA)
- Detection of specific auto-immune antibodies for systemic disorders, e.g., anti-ds DNA, rheumatoid factor, anti-histones, anti-Smith, anti-(SS-A) and anti-(SS-B)
- Detection of anti-RBC, antiplatelet, and anti-neutrophil antibodies
- Testing for organ-specific auto-immune antibodies, e.g., the anti-Islet cell autoantibody that is present in diabetes mellitus
- Coombs test (positive in autoimmune hemolytic anemia)

Allergic test

- Skin prick tests using various allergens from animal, plants, food, pathogens and environmental pollutants
- Radioallergosorbent test (RAST): Use to determine specific IgE antibodies

Treatment / Management

The treatment of immediate hypersensitivity reactions includes the management of anaphylaxis with intramuscular adrenaline (epinephrine), oxygen, intravenous (IV) antihistamine, support blood pressure with IV fluids, avoid latex gloves and equipment in patients who are allergic, and surgical procedures such as tracheotomy if there is severe laryngeal edema. Allergic bronchial asthma can be treated with any of the following: inhaled short- and long-acting bronchodilators (anticholinergics) along with inhaled corticosteroids, leukotriene antagonists, use of disodium cromoglycate, and environmental control. Experimentally, a low dose of methotrexate or cyclosporin and omalizumab (a monoclonal anti-IgE antibody) has been used. Treatment of autoimmune disorders (e.g., SLE) include one or a combination of NSAIDs and hydroxychloroquine, azathioprine, methotrexate, mycophenolate, cyclophosphamide, low dose IL-2, intravenous immunoglobulins, and belimumab. Omalizumab is a monoclonal antibody that interacts with the binding site of the high-affinity IgE receptor on mast cells. It is an engineered, humanized recombinant immunoglobulin. Moderate to severe allergic bronchial asthma can improve with omalizumab.

Differential Diagnosis

Allergic bronchial asthma must be ruled out from other classes of asthma based on the family history of atopy and a positive skin prick test. Chronic allergic bronchial asthma loses reversibility and is indistinguishable from chronic obstructive pulmonary disease (COPD).

Allergic rhinitis must rule out other causes of rhinitis including vasomotor, non-allergic rhinitis with eosinophilia, drug-induced (cocaine abuse), mechanical (tumors, foreign body, sarcoidosis) and infectious including viral, bacterial and leprosy. In allergic rhinitis, IgE is elevated, and prick test is positive for similar allergens as those in allergy bronchial asthma. Also, family predisposition to allergies may be present.

Autoimmune hemolytic anemia (AIHA) can rule out from other anemias based on the presence of a positive direct Coombs' test. Sometimes the AIHA is secondary to lymphoma or autoimmune disease, especially SLE, where other blood dyscrasias including immune thrombocytopenia and autoimmune neutropenia may be present besides with the presence of anti-dsDNA antibodies, and clinical signs including malar rash, nephropathy, vasculitis, serositis, neuropathy, and among other problems.

Prognosis

The prognosis of IHR depends on the severity of the disorders, the extension of the inflammation and tissue damage, and the available treatment and their effectiveness to control the disease. Relapsing or slow progression characterizes myasthenia gravis. If presents with thymoma, 68% of the affected have a 5-year survival. In SLE, approximately 80% survive at 15 years if treated. Atopic eczema (dermatitis) is usually most severe in infancy and improves with age in 80% of the cases. Allergic bronchial asthma that does not respond to steroids has a reserved prognosis.

The prognosis of other allergic disorders, including food allergy, drug allergy, latex allergy, allergic conjunctivitis, and allergic rhinitis is good once the triggers identified using skin prick test or RAST and treatment with anti-histamine occurs. The use of monoclonal antibodies directed to IgE (e.g., omalizumab) has improved the prognosis of patients that do not respond well to conventional therapy, although the acquisition of these biologicals is expensive. The use of vaccines, some classic and recently experimental, is another avenue of treatment of allergic disorders that improve the life expectancy and quality of individuals with allergies.

Complications

Some of the complications of immediate hypersensitivity reactions are:

Status Asthmaticus

This is a type I hypersensitivity reaction, an acute exacerbation of bronchial asthma that does not respond to the standard therapy with bronchodilators. It is a medical emergency and must require aggressive treatment.

Anaphylactic Shock

This is an allergic reaction, often life-threatening, triggered by an allergen to which the immune system over-reacts.

Post-Transfusion Reaction

This is a hypersensitivity reaction that occurs within 24 hours of a blood transfusion. Hemoglobinuria that appears during or after the procedure becomes an alarming sign. Other manifestations include back pain, fever, chills, dizziness, and dyspnea.

Serum Sickness

This is a type III hypersensitivity reaction that commences after the administration of a drug (e.g., penicillin) or heterologous anti-serum or plasma. Clinically, it is characterized by skin rash, fever, arthralgias, or arthritis. Immune-complexes mediate this complication, and it may affect many organs.

Deterrence and Patient Education

Healthcare professionals can advise allergic patients about environmental control at home and work. Every attempt to reduce high humidity and to decrease house dust-mite exposure must do. The bedroom should be clean, and many use mattress covers and wash bedclothes regularly. Pets, including cats and dogs, are often the source of allergens and should not be in convivence with the affected patient, nor should living plants and flowers, which are "a sack of antigens." Patients should be encouraged to explore therapeutic options for acute or chronic desensitization for "bad allergens." This may be the only way to control their allergic bronchial asthma.

Questions

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