HYPERSENSITIVITY

Hypersensitivity is in general, a state of increased reactivity to a foreign antigen or allergens. In another word, hypersensitivity is a set of undesirable reactions produced by the normal immune system including allergy and autoimmunity. The allergy is widely used to all forms of changed reactivity to antigenic stimulation whether the change in positive response or negative response. The negative response to the antigen is infact referred to as hypersensitivity. Moreover, the term allergic reaction nowadays refers to responses to certain environmental antigen suchas components of food, drugs, pollen and so on. It can lead to an inflammatory response with delterious effect ultimately result in tissue damage and even deatth. death. Portier and Rechet used the term anaphylaxis for this over or increased reactivity to the antegens.

The allergic or hypersensitivity reactions both reflects the expression of acquired immunologic responsiveness, involving specific antibodies and or T cells. most of the hypersensetive reactions are IgE medeated hypersensetive reactions. Hypersensitivity reactions require a presensitized state of the host.

The clinical aspect of classification of allergens is based on their origin, pattern of their distribution and or dissemination within the environment. Sensitization or induction of the hypersensetive state require several exposure to the allergens, followed by a latent period. After the latent period, a reaction is elicited by another exposure to the allergens. The nature of the hypersensitivity acquired is determined by the

chemical composition of the allergens, the sensitising route that may be injection, ingestion, inhalation and the physiology and anatomy of the host cell etc. The specific response observed depends upon the type of hypersensitivity and the mode of contact.

Robin Coombs and Philip Gell (1975) divided the hypersensitivity reactions into five types –

(I) Type I Hypersensitivity
(II) Type II Hypersensitivity
(III) Type III Hypersensitivity
(IV) Type IV Hypersensitivity
(V) Type V Hypersensitivity

Type I, II, and III hypersensitivity reactions are mediated by humoral immunity involving B cells and antibodies. They come under the purview of immediate hypersensitivity. Type IV hypersensitivity is delayed type of hypersensitivity (DTH). Type V hypersensitivity reaction is stimulatory hypersensitivity mediated by hormonal activity.

(I) Type I Hypersensitivity :→ Most of the allergic reactions occur due to type I hypersensitivity. In this type, the response usually occur within minutes after application or absorption of the allergens. Immediate reactions are associated with serum IgE antibodies and passive sensitization of a normal can be accomplished by transfer of serum from a sensitive or an immune individual. Anaphylaxis is a life threatening

either primary or secondary. The primary mediators are produced before degranulation and stored in the granules. The secondary mediators are are synthesized after Target cell activation. There are PAF, leukotrienes Prostaglandin and various cytokines. (Platelets aggravating factor)

Consequences of Type I reactions :→

consequences of type I reactions are life threatening systemic anaphylaxis and localized responses such as hay fever, asthma, rhinitis etc.

Diagnosis and treatment of Type I reactions

The diagnosis of the hypersensitivity is done by skin test involving mast cell and IgE. The reactions result in circumscribed edema and erythematous flare. To treat the hypersensitivity hypersensetization is done by repeated injection of increasing dose of allergens that reduce the severity due to shift of antibody response form IgE to IgG.

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Type II Hypersensitivity

Type II hypersensitivity are caused by specific IgM or IgG antibody. Type II reaction is manifested in blood transfusion patients and in autoimmune disease sufferers e.g Rhesus disease or haemolytic disease of the newborn. In this disease IgG antibody destory fetal red blood cells by antibody dependent cellular toxicity. Such antibody antigen binding result in cell destruction by FC fragment dependent mechanism directly or by classical complement pathway.

On the basis of type II reactivity Landsteiner (1900) classified human blood into groups.

Antigen bearing cells and tissues are damaged by IgG/IgM antibodies in association with complement. other effector cells like NK cells, Eosinophil cells, macrophage and neutrophils combine with Fc receptors. The polyclonal binding

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Type III Hypersensivity

Type III hypersensitivity is mediated by complement system and form immune complex. Complement protein C3a and C5a induce release of histamine and 5 hydroxy immune complex. The Complexes induce various chemotactic factors for the generation of free radicals, neutrophils, monocytes and macrophages and natural killer cells which causes cell and tissue damage. Deposition of immune complexes near the site of antigen entry can induce an Arthus reaction in which lyter enzymes released by the accumulated neutrophils and complement membrane attack complex. The manifestation of these reactions vary depending on the site of tissue deposition. Type III hypersensitivity is of two types i Localized type III reactions and generalized type III reactions.

In former type the high level of circulating antibodies produced by injection of antigen leads to formation of immune complex within 4-8 hrs. As the reaction proceeds, localized tissue and vascular damage results by an accumulation of fluid (edema) and red blood cell (erythma) at the site. It is Known as Arthus reaction.

In generalized type III reactions immune complex stimulate complements, aggregation of platelets and release of vasoactive amines affecting permeability of endothelial cells. Typically, within days or weeks after exposure to serum foreign antigens a combination of symptoms appear that are called Serum sickness. These are fever, weakness, rashes, edema, erythema, arthritis etc.

Systemic reaction that occur in sensitized individual within minutes of exposure to allergens.

Various component of Type I hypersensitivity comprises:

(I) Response of IgE to antigens or allergens
(II) Role of IgE receptors.
(III) Response of mast cells to allergens.
(IV) Mediators of type I reactions.
(V) Consequences of type I reaction
(VI) Diagnosis and treatment of type I reaction.

(I) Response of IgE to antigens and allergens:-

Allergens that can elicit IgE production by specific B cell or Plasma cells are foreign, serum, egg albumin, pollen, drugs parasites and even a non parasite antigens. Allergens normally enter the body at very low doses by diffusion across mucosal surface. The production of IgE by allergen-specific B cell is facilitated by CD4 TH2 (Helper cell) and IL4 and IL3 respectively. The specific IgE produced binds to the high affinity receptor for IgE on mast cell, basophils and activated ~~receptors~~ eosinophils. These cells can amplify IgE over production. because The IgE over production is influenced by genetic and environmental factors. IgE has a short halflife (2-3 days) however when bound to cells its lifetime increases to several weeks.

High affinity FCεRI and low affinity FCεRII. FCεRI present on mast cell and basophils. Allergens cross link IgE and aggregates FCεRI and activates B cell to produce IgE. The low affinity receptor present on the cell surface of natural killer cells (NK cells) macrophages, dendritic cell, eosinophil cells and platelets.

Response of mast cell to antigens:→

Mast cell of both kind ie connective tissue mast cell and mucosal mast cell remain throughout the body. Mast cell bounds with IgE with antigen makes 2 or 3 cross linkage with FCεRI a series of reactions are activated. Activated mast cell initiates various signal transduction pathways. The mast cell granules release histamine, Serotonin, platelet activating factor, bradykinin etc. These act as strong vasodilator. Mast cell also produce chemotactic factor for anaphylaxis. Thus mast cell function as store house for interleukins (IL4, 5 and IL8), granulocyte macrophage and colony stimulating factor

The IgE mediated activation of mast cell, basophil and eosinophils provide protection against single or multiple infections.

Mediator of Type I reaction:— These mediators are pharmacologically active agents that act on local tissues as well as on populations of secondary effector cells, like eosinophil, neutrophil, T lymphocyte, monocytes and platelets.

The mediators are classified as

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Type IV hypersensitivity

Type IV hypersensitivity reactions are mediated by T cells. T cells recognize antigens in association with MHC molecules. In type IV hypersensitivity antigens activate sensitizes T_H (CD4 CD8) cells, which release interleukins (IL) IFNγ (Interferon gamma), MIF (macrophage inhibition factor and TNFβ (Tumour necrosis factor). The overall effect of these cytokines is to draw macrophages into the area and activates them, promoting increased phagocytic activity and increased conc^n of lytic enzymes for more effective killing. These reactions typically take 48-72 hrs to develop hence it is called as cell mediated immunity or delayed Type of hypersensitivity reaction. Type IV hypersensitive reaction is important in host defence against parasites and bacteria that can live within cells. The heightened phagocytic activity and the buildup of lytic enzymes from macrophages in the area of infection lead to nonspecific destruction of cells and thus of the intracellular pathogens. The continued presence of the pathogen's antigen can provoke a chronic DTH reaction, which is characterized by excessive number of macrophage continual release of lytic enzymes and consequent tissue destruction. The type IV hypersensitivity reaction cause tissue damage consisting of (I) contact hypersensitivity (II) Tuberculous type hypersensitivity reaction (III) Granulomatous hypersensitivity and (IV) cellular reactions. Tissue damage feature of type IV hypersensitivity comprise immunopathological changes in leprosy, measels, herpes, leishmaniasis, fungal disease and dermatitis disease.