CHAPTER

8

HYPERSENSITIVITY

Objectives:

- Have a basic knowledge about different types of hypersensitivity.
- Be familiar with the mechanism, pathogenesis of each type.
- Be aware of clinical features of each type.
- Be able to diagnose each type.
- Understand the concept of therapy.

Hypersensitivity reactions is a state of tissue damage results from immune reaction to further dose of antigen in previously immunized individual.

Types of hypersensitivity:

Hypersensitivity reactions were divided into four types:

1. Type I, IgE mediated reactions , also called immediate hypersensitivity or allergy)
2. Type II, Cytolytic or cytotoxic reactions .
3. Type III, Immune complex reactions.
4. Type IV, Cell-mediated immunity (CMI) reactions also called delayed-type hypersensitivity (DTH) e.g. microbial hypersensitivity and contact dermatitis.

Type (I) Hypersensitivity

[Immediate Hypersensitivity Reactions]

- It is immediate hypersensitivity reaction.
- It is initiated by antigens reacting with cell bound IgE.
- It is manifested in many ways (dependent on the organ or tissue involved).
- It may range from atopic allergy (e.g. food allergy or hay fever) to fatal anaphylactic shock.

- **Allergens**: are antigens that induces production of specific IgE e.g. plant pollens, mould, spores, animal hair, house dust, foreign serum, some foods (fish, egg, milk) and some drugs as penicillin.
- **Reaginic antibody** IgE antibody which is produced in response to a specific allergen.

Mechanism of type 1- hypersensitivity

1) As soon as IgE is synthesized after the first challenge with Ag it becomes bound to Fc receptors on basophils and mast cells.
2) Binding of IgE to cell membranes increase the half –life of IgE from 2 or 3 days up to 14 days .
3) Once bound, IgE serves as an antigen receptor on mast cells and basophils.
4) In the second challenge with the same Ag, the Ag bound to 2-3 IgE, this is called **cross – linking** of antibody molecules. This induces degranulaion of mast cells and release of two kinds of mediators:

- **Preformed mediators** such as:

  Histamine and chemotactic factor are the mediators of symptoms seen during the early phase , which occurs within 15-20 minutes of exposure to the allergen.

  Newly formed mediators: Leukotrines, platelet activating factor (PAF) and prostaglandins, which take several hours to be synthesized, cause the symptoms seen during the late phase. The late phase typically occurs 5-6 hours after allergen contact the symptoms of the late phase are the same as those of the early phase. But persist longer.

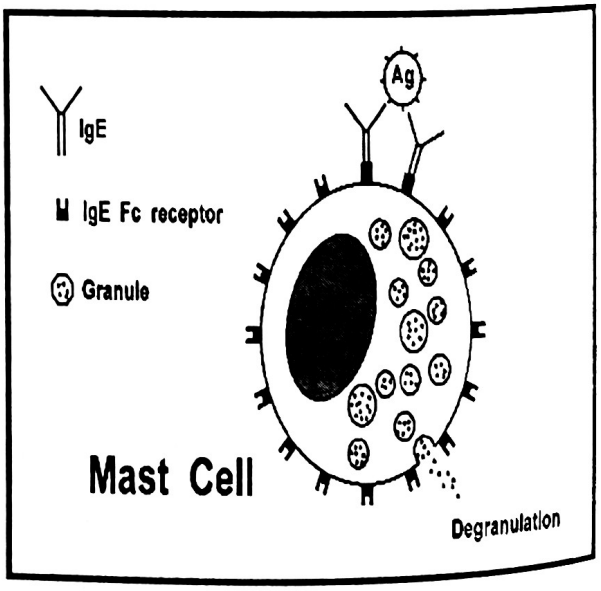

Figure (14):Mast cell degranulation.

- The late phase involves the recurriment of other effector cells, notably TH2 lymphocytes, eosinophils and basophils which contribute significantly to the inflammatory response and tissue damage.

N.B.

- Th-2 subset secrete IL-4 which is required for immunoglobulin switching to IgE, , and secrete IL-5 which. promotes activation of eosinophiles .
- Eosinophils is also attracted to the site of reaction by a chemotactic factor released by the mast cell and basophils.
- Eosinophils release histaminase and phospholipase D , these degrade histamine , so eosinophils act as a internal negative control mechanism.
- Because immediate hypersensitivity reactions are dependent on T-cells, T-cell - independent antigens such as polysaccharides cannot elicit such reactions unless they become attached to proteins.

Types of immediate hypersensitivity reactions

Anaphylaxis is the most rapid type of hypersensitivity , it can be generalized or localized (cutaneous).

A- Generalized (systemic) anaphylaxis

- Generalized (systemic) anaphylaxis occurred in certain conditions after parenteral injection of a foreign antigen. The anaphylaxis occurs when a second dose of the same antigen is introduced into the body after a period 2-3 weeks later. The anaphylactic shock is usually fatal.
- In man anaphylaxis presents with itching , erythema , vomiting , abdominal cramps , diarrhea and respiratory distress. In severe cases laryngeal edema and vascular collapse may results in death.

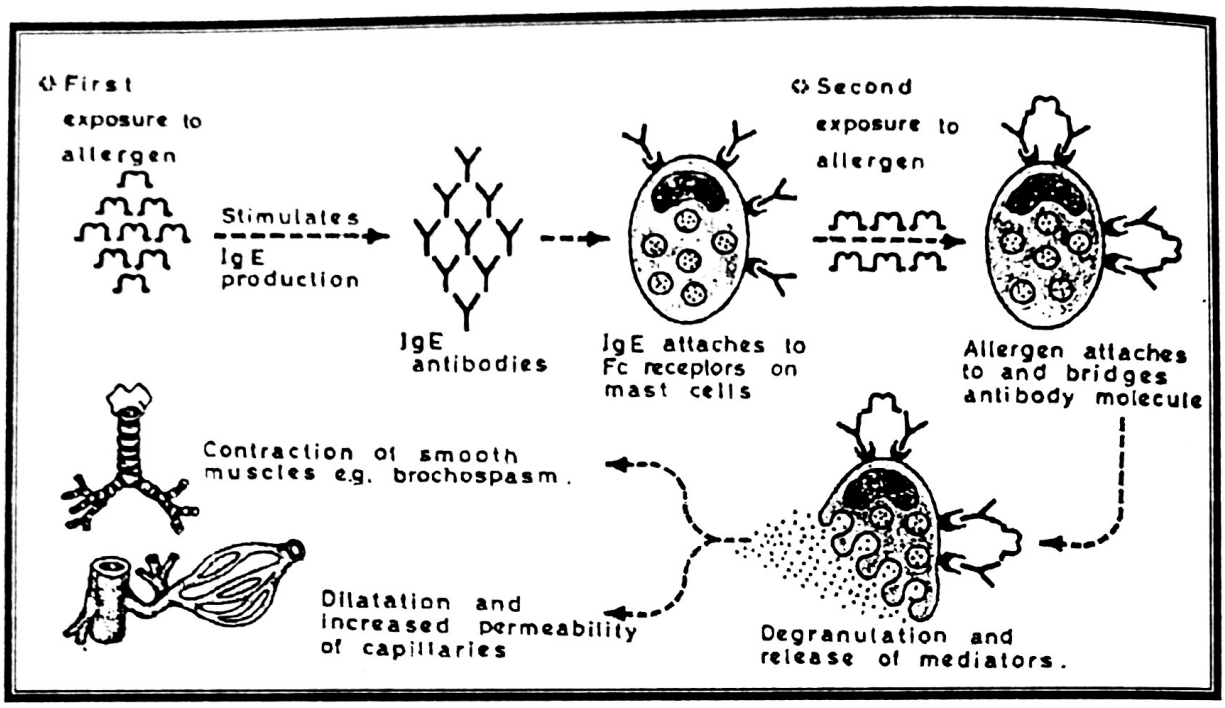

Figure (15) : Mechanisms of type I hypersensitivity reactions

(B) Localized anaphylaxis:(Atopy):

Atopy is the local form of type I hypersensitivity reactions affecting one organ. It occurs on exposure to certain allergens that induce production of specific IgE. These include:

- Inhalants e.g. house dust, house dust mite, pollens, moulds spores.
- Ingestants e.g. milk, wheat, egg, fish, strawberries, chocolate.
- Contactants e.g. wool, animal fur, nylon.

There is a strong familial predisposition to the development of atopic allergy. The predisposition is **genetically** determined. Such individuals have the ability to produce high levels of IgE. Different members of a family may manifest in different ways.

The manifestations depend on the site of antigen antibody reaction. If it occurs in the bronchial tree, this will lead to bronchial asthma, if in the nose it will cause rhinitis or hay fever. If in the gastrointestinal tract it will cause diarrhea and vomiting. If it occurs in the skin it will result in urticaria and skin rash, if in the eye it will cause conjunctivitis.

Methods of Diagnosis:

1. Skin tests: These are done by intradermal injection of a battery of different groups of allergens. A wheal and erythema develops within 15-25 minutes at the site of the allergen to which the individual is allergic.
2. Determination of total serum IgE level which is usually high in atopic individuals by ELISA.
3. Determination of specific IgE levels to the different allergens by ELISA.
4. Provocation tests may be used, by challenging the patient with the allergen, in question, intranasal or otherwise.

Management:

A. Management of anaphylactic shock:

Anaphylactic shock is an emergency which must be dealt with immediately by administration of adrenaline, corticosteroids together with oxygen inhltion.

B. Management of atopy

a. Avoidance of the specific allergen responsible for the condition e.g. food and drug allergies.

b. Desensitization: Weekly administration of the Ag to which the person is hypersensitive. This stimulates the production of IgG blocking antibodies in serum which can prevent subsequent Ag from reaching IgE on the mast cells, thus preventing the reaction.

c. Drugs that block the release of the mediators or counteract their effect e.g. corticosteroids, anti-histaminics, anti-leukotrienes.

Type II hypersensitivity

(Cytotoxic OR cytolytic reaction)

Mechanism:

- Occurs when Ab (IgM or IgG) reacts with antigen on the cell surface.
- Binding of specific antibody directly to the antigen on the cell surface produce damage to that cell through three pathways:

1- Antibody (IgM or IgG) activates the complement leading to cell lysis by membrane attack unit (MAC).

2- IgG usually serve to engage receptors on phagocytic cells for Fc and C3b, this leads to phagocytosis and destruction of the cell by macrophages and neutrophils.

3- Antibody coated cells can be killed by several cells having Fc receptor. The cells most active (in ADCC) are macrophages and NK cells. These reactions occurs within hours of re-exposure.

Examples of diseases caused by type II hypersensitivity:

1- Transfusion reaction e.g. ABO incompatibility RH incompatibility.
2- Auto-immune hemolytic disease of the new born (erythroblastosis fetalis).
3- Auto immune hemolytic anemia.
4- Idiopathic thrombocytopenic purpura.
5- Drug reaction: The drug act as a hapten and is attached to the cell surface and induce cytotoxicity e.g. penicillin is attached to RBCs leading to hemolytic anemia, quinine and phenacetin attached to platelets leading to thrombocytopenic purpura.
6- Rheumatic fever (post streptococcal infection).

Type III, Hypersensitivity

(Toxic complex syndrome)

- It is a hypersensitivity reaction that characterized by formation of antigen antibody complex.

Mechanism:

- Immune complex (Ics) mediated reactions are initiated by antigen antibody immune complexes that either are formed locally (at the site of tissue damage) or deposited from the circulation.
- The reaction start by formation of soluble antigen – antibody complexes with antigen excess the immune complex escape phagocytosis penetrate the endothelium of blood vessel walls and are deposited on the vascular basement membrane.
- Complement is activated with the release of factors that are chemotactic for neutrophil (e.g. C5a).

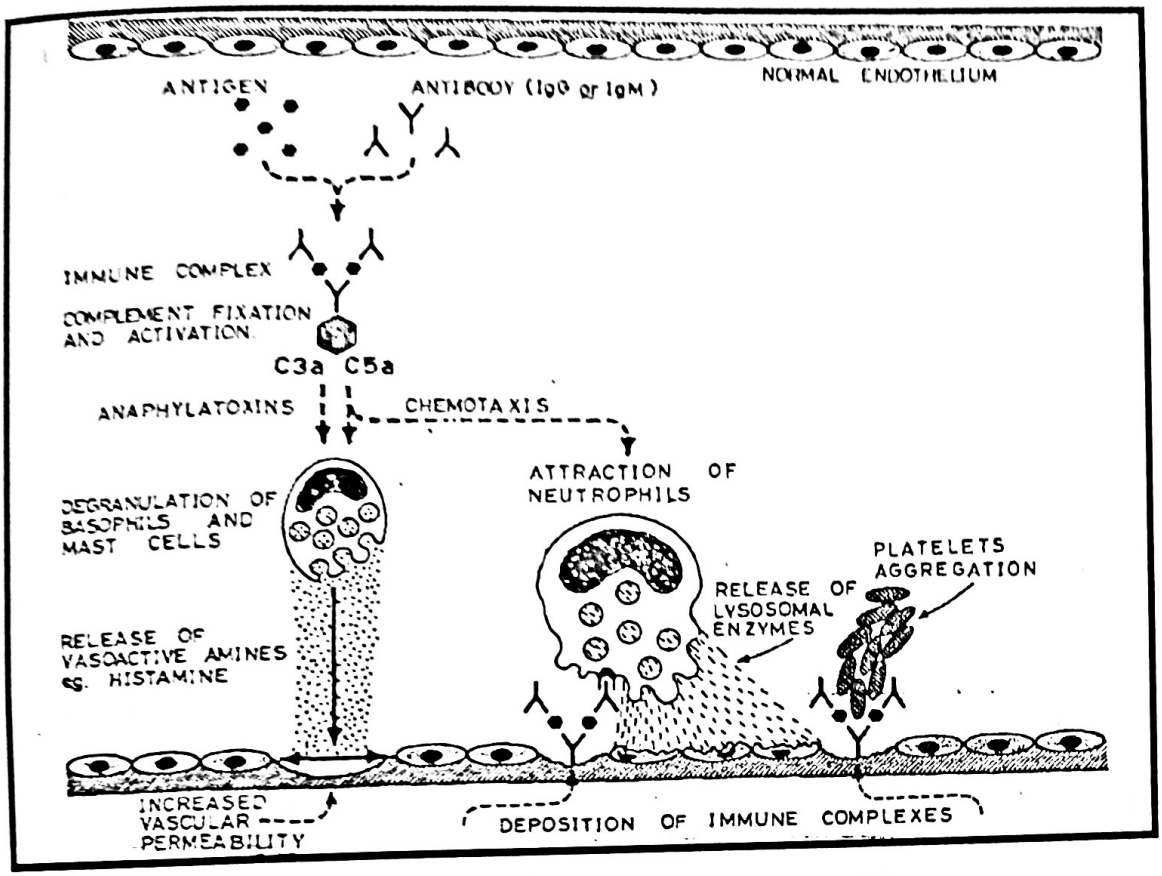

Figure (16) : Mechanism of type III hypersensitivity

- The neutrophils then infiltrate the area and release lysosomal enzymes that destroy the basement membrane.

Clinical types:

A- Systemic immune complex disease

1- Serum sickness:

- **Definition:** it is a systemic immune – complex reaction follows the injection of foreign serum into human (e.g. Diphtheria antitoxins).
- **Etiology:** This form of serum reaction may develop after a single dose of foreign serum for the first time (not two doses as in anaphylaxis).
- **Mechanism:** The reaction occurs after 10 – 15 days (a period allowed antibody formation) formed antibodies will react with a fraction of the same antigen still diffusing from a fixed fraction of the foreign serum at the site of injection leading to immune – complexes formation which are deposited in the tissue.

- Characterized by fever, rash, splenomegaly, lymphadenopathy, arthritis and glomerulonephritis.

2- Post streptococcal glomerulonephritis:

- It is an immune complex glomerulonephritis due to immune complex deposition in the renal vasculature.
- Characterized by proteinuria, hematuria and RBCs casts in the urine.

3- Autoimmune disease:

- Endogenous antigen – antibody – complement complexes are involved in the pathogenesis of some autoimmune diseases as rheumatoid arthritis and SLE.

B- Local immune complex diseases: Arthus reaction:

These reactions may **occur in diabetics** receiving repeated subcutaneously injections of insulin or after **rabies vaccination.**

When the same antigen is repeatedly injected intradermally or subcutaneously, it combines with specific antibody from the blood to form local immune complexes After 2 or 3 injections , Ics are deposited in the small blood vessels leading to vasculitis, microthrombi , vascular occlusion and necrosis. These reactions are manifested by edema, erythema and necrosis

Management of immune complex diseases

1. Reduction of inflammation by means of antihistaminics and corticosteroids.
2. Suppression of the immune response by means of corticosteroids and immunosuppressive drugs.
3. Removal of offending complexes via plasmapheresis (exchanging the patient's plasma with normal plasma, thereby removing the immune complexes).

Detection of immune complexes:

* **In tissues**: by staining tissue biopsies with fluorescein labeled anti-C3 or anti-IgG or anti-IgM.
* **In serum** by:
  a- Measuring the levels of C3, which may decrease.
  b- Precipitation of immune complexes and determination of the amount of IgG in the precipitate.

c- Estimation of binding of immune complexes to Clq: C1q is linked to a solid phase support Raji cells: A human lymphoblastoid cell line that binds IC through C3 receptors.

Type IV Hypersensitivity

(Delayed or cell – mediated reactions)

- It is an exaggerated cell mediated immune response that damages host cells. It is initiated by sensitized (antigen – reactive) T – cells (T4 & T8) reacting with the specific antigens.
- In DTH the effector cells are[the activated macrophage (M Ø) , TH-1 cell & CTLs].
- The enhancement of microbicidal function of phagocytes is mediated by T helper-1 cell cytokines **mainly IFN γ.**
- DTH reactions take **many hours (18-24hours)** to occur after contact with antigen and often **lasts for days.** It is manifested as inflammation with induration at the site of antigen exposure and reaches a peak after 24 – 48 hours.
- The clinical loss of DTH , is an indication of deficient T- cell function , a condition known as **anergy**. This loss of immune responsiveness should be distinguish from **"clonal anergy"** , which is a mechanism needed for maintaining tolerance to self antigens.
- Tissue damage results from the interaction between sensitized T –cells and the specific antigen, with releasing of soluble effector substances called lymphokines.

Clinical Conditions due to DTH

- **Protective DTH Response : DTH to intracellular bacterial antigens .**

Granulomatous Reactions :

- This type of CMI is a part of the primary defense mechanism against intracellular pathogens such as ; Listeria monocytogenes , Mycobacteria

and Shistosoma, where there is a persistent stimulus in which macrophages cannot eliminate these pathogens. Such microbes cannot be killed by normal unactivated phagocytes, and even survive within the phagolysosomes. Eradication of these organisms requires enhancement of microbicidal function of phagocytes by T helper1- cell cytokines (IFN-γ , IL -2 , LT & TNF) resulting in induction of mmunological granulomas .

In-vivo Skin tests of DTH :

-**Tuberculin test .**

- **Brucellin test** in brucellosis
- **Lepramin test** in leprosy.
- **Frei's test** in lymphogranuloma venerium.

-**Candidin test** in candida infections.

Tuberculin Test

- In this test a purified protein derivative (PPD) [a protein prepared from mycobacterium tuberculosis], will elicit a DTH response when injected intradermal into individuals who have recovered from primary tuberculosis ,or who have been vaccinated against tuberculosis.
- The characteristic response of DTH evolves over 24 to 48 hours with the appearance of induration at the site of injection . The lag in the onset of palpable induration is due to the time needed for accumulation of activated immune cells and deposition of fibrin which cause the tissue to swell and become hard (" indurated") and this is the reason for calling the response " **delayed type**".

Non protective DTH: DTH to non- bacterial antigens:

Contact Dermatitis:

The same sequence of T-cell and M Ø activation can be elicited by contact sensitization with non microbial products .This occurs due to contact of the skin with chemical substances or drugs , nickel salts (as in nickel jewelry) ,

hair dyes, cosmetics , soaps . etc. These substances enter the skin in small molecules and act as haptens attach to body proteins to serve as complete antigens. DTH reaction to these substances will lead to an inflammatory reaction of the skin in the form of eczema, rash and vesicular eruptions. In these situations, activation of M Ø can cause **tissue injury** without providing protective function, **hence the term " hypersensitivity"**

Treatment:

Topical steroid may be used. Otherwise, systemic corticosteroids may be administered.