Hypersensitivity

By: Dr. Suzan Yousif
Classification

• Coombs and Gell classification

1- Type I - anaphylactic (atopic, or immediate)
2- Type II - cytotoxic (antibody-dependent)
3- Type III - immune complex
4- Type IV - delayed or cell-mediated
Type I hypersensitivity is also known as immediate or anaphylactic hypersensitivity.

The reaction may involve skin (urticaria and eczema), eyes (conjunctivitis), nasopharynx (rhinitis), bronchopulmonary tissues (asthma) and gastrointestinal tract (gastroenteritis).
• The reaction may cause a range of symptoms from minor inconvenience to death.

• The reaction usually takes 15 - 30 minutes from the time of exposure to the antigen.

• sometimes it may have a delayed onset (10 - 12 hours).
• Immediate hypersensitivity is mediated by IgE.
• The primary cellular component in this hypersensitivity is the mast cell or basophil.
• The reaction is amplified and/or modified by platelets, neutrophils and eosinophils.
• A biopsy of the reaction site demonstrates mainly mast cells and eosinophils.
Mechanism:

- The mechanism of reaction involves preferential production of IgE, in response to certain antigens (allergens).
- IgE has very high affinity for its receptor on mast cells and basophils.
- A subsequent exposure to the same allergen cross links the cell-bound IgE and triggers the release of various pharmacologically active substances like histamine, heparin tryptase, chymase, and monocyte chemotactic factors.
① First exposure to pollen stimulates B cells to produce “allergy” plasma cell.

② Plasma cells produce allergy antibodies.

③ Allergy antibodies bind to mast cells.

④ Re-exposure to pollen results in pollen binding to allergy antibodies on mast cells.

⑤ Binding of pollen stimulates mast cells to release histamine, triggering the inflammatory response.
# Allergens

## Table 16-1: Common Allergens Associated with Type I Hypersensitivity

<table>
<thead>
<tr>
<th>Proteins</th>
<th>Foods</th>
<th>Plant pollens</th>
<th>Insect products</th>
<th>Drugs</th>
<th>Mold spores</th>
<th>Animal hair and dander</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign serum</td>
<td>Nuts</td>
<td>Rye grass</td>
<td>Bee venom</td>
<td>Penicillin</td>
<td>Cockroach calyx</td>
<td></td>
</tr>
<tr>
<td>Vaccines</td>
<td>Seafood</td>
<td>Ragweed</td>
<td>Wasp venom</td>
<td>Sulfonamides</td>
<td>Dust mites</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eggs</td>
<td>Timothy grass</td>
<td>Ant venom</td>
<td>Local anesthetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peas, beans</td>
<td>Birch trees</td>
<td>Cockroach calyx</td>
<td>Salicylates</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Milk</td>
<td></td>
<td>Dust mites</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Insect products</td>
<td></td>
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</tr>
</tbody>
</table>
## Contents of the Mast Cell Granules

<table>
<thead>
<tr>
<th>Active agent</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>Increases vascular permeability; elevates level of cyclic AMP</td>
</tr>
<tr>
<td>Heparin</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Increases vascular permeability</td>
</tr>
<tr>
<td>Chymase</td>
<td>Proteolysis</td>
</tr>
<tr>
<td>Hyaluronidase</td>
<td>Increases vascular permeability</td>
</tr>
<tr>
<td>Eos. Chem. Factor</td>
<td>Chemoattraction of eosinophils</td>
</tr>
<tr>
<td>Neut. Chem. Factor</td>
<td>Chemoattraction of neutrophils</td>
</tr>
<tr>
<td>Platelet Agg. Factor</td>
<td>Aggregates platelets</td>
</tr>
</tbody>
</table>
Localized anaphylaxis

Target organ responds to direct contact with allergen.

• **Digestive tract** contact results in vomiting, cramping, diarrhea.

• **Skin** sensitivity usually inflamed area resulting in itching.

• **Airway** sensitivity results in sneezing and rhinitis OR wheezing and asthma.
Systemic anaphylaxis

- Systemic vasodilation and smooth muscle contraction leading to severe bronchiole constriction, edema, and shock.

- Similar to systemic inflammation.
Treatment for Type I

• Pharmacotherapy Drugs.
  – Non-steroidal anti-inflammatory drugs
  – Antihistamines block histamine receptors.
  – Steroids
  – Theophylline OR epinephrine - prolongs or increases cAMP levels in mast cells which inhibits degranulation.
Treatment for Type I

• Immunotherapy
  – Desensitization (regular administration of gradually increasing doses of allergen extracts over a period of years)
  – Repeated injections of allergen to reduce the IgE on Mast cells and produce IgG.
TYPE II HYPERSENSITIVITY
cytoxic

- Type II hypersensitivity is also known as antibody-dependent hypersensitivity and may affect a variety of organs and tissues.
- In type II hypersensitivity, the antibodies produced by the immune response bind to antigens on the patient's own cell surfaces.
- The antigens recognized in this way may either be intrinsic ("self" antigen, innately part of the patient's cells) or extrinsic (absorbed onto the cells during exposure to some foreign antigen, possibly as part of infection with a pathogen.
• IgG and IgM antibodies bind to these antigens to form complexes that activate the classical pathway of complement activation for eliminating cells presenting foreign antigens.

• As a result mediators of acute inflammation are generated at the site and membrane attack complexes cause cell lysis and death. The reaction takes hours to a day.
Examples

• Autoimmune haemolytic anaemia
• Pernicious anemia
• Immune thrombocytopenia
• Transfusion reactions
• Hashimoto's thyroiditis
• Graves' disease
• Myasthenia gravis
• Hemolytic disease of the newborn
Blood Transfusion reactions

The ABO Blood System

<table>
<thead>
<tr>
<th>Blood Type (genotype)</th>
<th>Type A (AA, AO)</th>
<th>Type B (BB, BO)</th>
<th>Type AB (AB)</th>
<th>Type O (OO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Blood Cell Surface Proteins (phenotype)</td>
<td>A agglutinogens only</td>
<td>B agglutinogens only</td>
<td>A and B agglutinogens</td>
<td>No agglutinogens</td>
</tr>
<tr>
<td>Plasma Antibodies (phenotype)</td>
<td>b agglutinin only</td>
<td>a agglutinin only</td>
<td>No agglutinin</td>
<td>a and b agglutinin</td>
</tr>
</tbody>
</table>
Hemolytic disease of newborn

Rh factor incompatibility

- IgG abs to Rh an innocuous RBC antigen
  - Rh\(^+\) baby born to Rh\(^-\) mother first time fine. 2nd time can have abs to Rh from 1st pregnancy.
  - Ab crosses placenta and baby kills its own rbcs.
  - Treat mother with ab to Rh antigen right after birth and mother never makes its own immune response.
Rh factor incompatibility

1. Rh⁺ father.
2. Rh⁻ mother carrying her first Rh⁺ fetus. Rh antigens from the developing fetus can enter the mother's blood during delivery.
3. In response to the fetal Rh antigens, the mother will produce anti-Rh antibodies.
4. If the woman becomes pregnant with another Rh⁺ fetus, her anti-Rh antibodies will cross the placenta and damage fetal red blood cells.
TYPE III HYPERSENSITIVITY

immune complexes

- Large amount of antigen and antibodies form complexes in blood.
- If not eliminated can deposit in Kidneys, Joints, Lung, Skin and trigger inflammation.
- PMNs and macrophages bind to immune complexes via FcR and phagocytize the complexes.
- If unable to phagocytize the immune complexes can cause inflammation via C’ activation.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Antigen involved</th>
<th>Clinicopathologic manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>DNA, nucleoproteins, others</td>
<td>Nephritis, arthritis, vasculitis</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Hepatitis B virus surface antigen</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Poststreptococcal glomerulonephritis</td>
<td>Streptococcal cell wall antigen(s); may be &quot;planted&quot; in glomerular basement membrane</td>
<td>Nephritis</td>
</tr>
<tr>
<td>Serum sickness</td>
<td>Various proteins</td>
<td>Arthritis, vasculitis, nephritis</td>
</tr>
</tbody>
</table>
Serum sickness

- Is a disease caused by the injection of large doses of a protein antigen into the blood and characterized by the deposition of antigen-antibody complexes in blood vessel walls, especially in the kidneys and joints.
Systemic Lupus Erythmatosus

• The disease is characterized by the presence of autoantibodies, which form immune complexes with autoantigens and are deposited within the kidney glomeruli.

• The resulting type III hypersensitivity is responsible for the glomerulonephritis (Inflammation of blood capillary vessels in the glomeruli).
1. Genes

C1q,C2,C4
HLA-D2,3,8
MBL
FcR 2A,3A,2B
IL-10
MCP-1
PTPN22

2. Abnormal Immune Response

DC
Ag
T cell
B cell
C3
C3a

3. Autoantibodies

Immune Complexes

Defective suppressive networks

4. Inflammation

Rash
Nephritis
Arthritis
Leukopenia
CNS dz
Carditis
Clotting
Etc.

5. Damage

Renal Failure
Atherosclerosis
Pulm fibrosis
Stroke
Damage from Rx
Etc.

Environment

UV light
Gender
Infection
EBV
Others

Butterfly rash
TYPE IV HYPERSENSITIVITY

Delayed type hypersensitivity

• DTH response is from:
  – Th1 cells release cytokines to activate macrophages causing inflammation and tissue damage.
  – Continued macrophage activation can cause chronic inflammation resulting in tissue lesions, scarring, and granuloma formation.

• Delayed is relative because DTH response arise 24-72 hours after exposure rather than within minutes.

• Unlike the other types, it is not antibody mediated but rather is a type of cell-mediated response.
Stages of Type IV DTH

Sensitization stage

• Memory Th1 cells against DTH antigens are generated by dendritic cells during the sensitization stage.

• These Th1 cells can activate macrophages and trigger inflammatory response.
Stages of Type IV DTH

**Effector stage**

- Secondary contact yields what we call DTH. **Th1** memory cells are activated and produce cytokines which cause tissue destruction, inflammation.
- Inflamed area becomes red and fluid filled can form lesion.
- Continued exposure to antigen can cause chronic inflammation and result in granuloma formation.
Delayed type hypersensitivity (DTH)

DTH can be the result of Chronic infection or Exposure to some antigens.

<table>
<thead>
<tr>
<th>TABLE 14-3 INTRACELLULAR PATHOGENS AND CONTACT ANTIGENS THAT INDUCE DELAYED-TYPE HYPERSENSITIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracellular bacteria</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>Mycobacterium leprae</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
</tr>
<tr>
<td>Brucella abortus</td>
</tr>
<tr>
<td>Intracellular fungi</td>
</tr>
<tr>
<td>Pneumocystis carinii</td>
</tr>
<tr>
<td>Candida albicans</td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
</tr>
<tr>
<td>Intracellular parasites</td>
</tr>
<tr>
<td>Leishmania sp.</td>
</tr>
<tr>
<td>Intracellular viruses</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
</tr>
<tr>
<td>Variola (smallpox)</td>
</tr>
<tr>
<td>Measles virus</td>
</tr>
<tr>
<td>Contact antigens</td>
</tr>
<tr>
<td>Picrylchloride</td>
</tr>
<tr>
<td>Hair dyes</td>
</tr>
<tr>
<td>Nickel salts</td>
</tr>
<tr>
<td>Poison ivy</td>
</tr>
<tr>
<td>Poison oak</td>
</tr>
</tbody>
</table>
Type IV DTH
Contact dermatitis

• The response to poison oak is a classic Type IV.
  – Small molecules act as haptens and complex with skin proteins to be taken up by APCs and presented to Th1 cells to get sensitization.
  – During secondary exposure Th1 memory cells become activated to cause DTH.
Contact dermatitis

Poison oak
(*Toxicodendron radicans*)

Pentadecacatechol

Skin

Self-protein
Sensitized TDTH

IFN-\(\gamma\)

Langerhans cell (APC)

MIF

MCF

Lytic enzymes

Tissue macrophage

Monocyte
Drug reactions can be any Type of Hypersensitivity

<table>
<thead>
<tr>
<th>Type of reaction</th>
<th>Antibody or lymphocytes induced</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IgE</td>
<td>Urticaria, systemic anaphylaxis</td>
</tr>
<tr>
<td>II</td>
<td>IgM, IgG</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>III</td>
<td>IgG</td>
<td>Serum sickness, glomerulonephritis</td>
</tr>
<tr>
<td>IV</td>
<td>$T_{DTH}$ cells</td>
<td>Contact dermatitis</td>
</tr>
</tbody>
</table>
# Immune-Mediated Hypersensitivities

<table>
<thead>
<tr>
<th>Type</th>
<th>Immune Reactant</th>
<th>Antigen</th>
<th>Effector Mechanism</th>
<th>Example of Hypersensitivity Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IgE antibody, T(_{H2}) cells</td>
<td>Soluble antigen</td>
<td>Mast-cell activation</td>
<td>Allergic rhinitis, asthma, systemic anaphylaxis</td>
</tr>
<tr>
<td>II</td>
<td>IgG antibody</td>
<td>Cell- or matrix-associated antigen</td>
<td>Complement, FcR(^{+}) cells (phagocytes, NK cells)</td>
<td>Some drug allergies (e.g., penicillin)</td>
</tr>
<tr>
<td>III</td>
<td>IgG antibody</td>
<td>Soluble antigen</td>
<td>Complement Phagocytes</td>
<td>Serum sickness, Arthus reaction</td>
</tr>
<tr>
<td>IV</td>
<td>T cells</td>
<td>Soluble antigen</td>
<td>Macrophage activation</td>
<td>Contact dermatitis, tuberculin reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cell-associated antigen</td>
<td>Cytotoxicity</td>
<td>Contact dermatitis</td>
</tr>
</tbody>
</table>