Medical Immunology for M.D. Students

Hypersensitivity Reactions (2)

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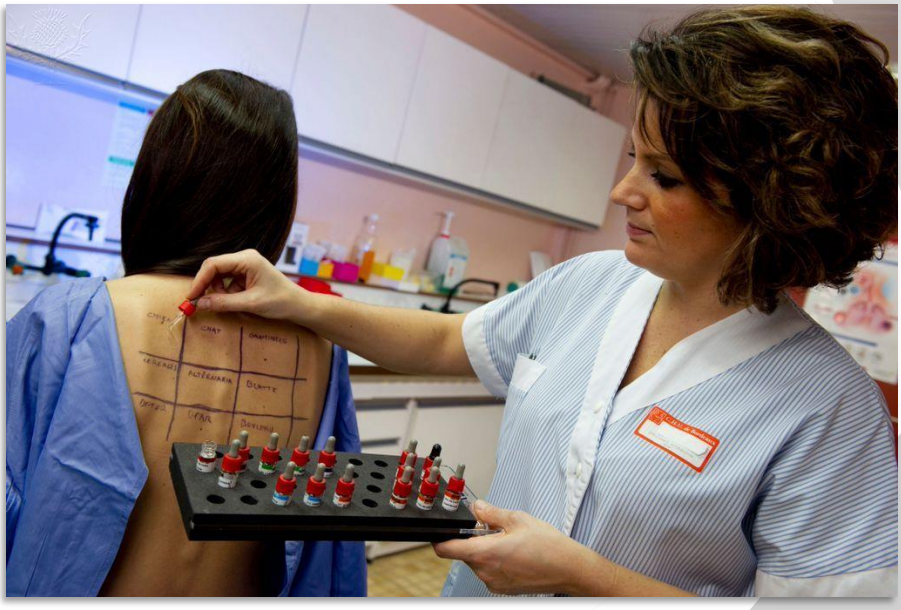
Mechanisms and classification of HSRs

Type	*Immune mediator of pathology*	*Mechanism of tissue injury*	*Examples*
Immediate (type I)	IgE	Mast cells and their mediators (vasoactive amines, lipid mediators and cytokines)	Allergic reactions, anaphylaxis, asthma
Antibody mediated (type II)	IgM, IgG against cell surface or extracellular matrix antigens	Phagocytosis, Ab-dependent cell mediated cytotoxicity (ADCC), receptor blocking or complement mediated lysis	Goodpasteur's syndrome, ABO incompatibility, Rh incompatibility
Immune complex mediated (type III)	Circulating immune complexes of antigens and IgM or IgG	Ag-Ab complexes activate the complement and Fc receptors resulting in activation and recruitment of leukocytes	Poststreptococcal glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis
Cell mediated (type IV)	CD4+ T cells or CD8+ cytotoxic T lymphocytes (CTLs)	Macrophage activation resulting in cytokine mediated inflammation or direct cell killing by CTLs	Contact dermatitis, tuberculosis

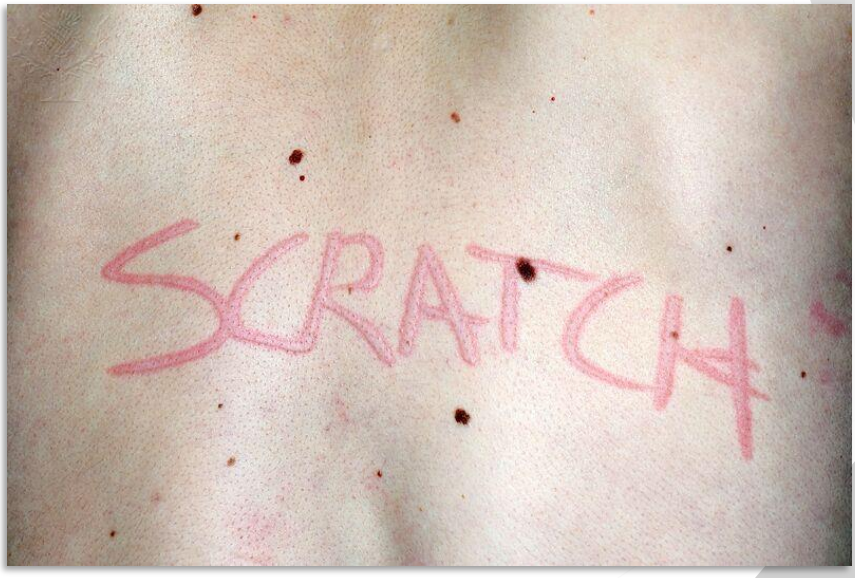
Anaphylaxis

- Anaphylaxis is a systemic type 1 (IgE-mediated, immediate) HSR.
- The word anaphylaxis is recognized and feared by most health care providers because of its association with potential death from cardiovascular collapse or asphyxiation caused by laryngeal edema.
- As with other type I HSR examples, the first exposure to an allergen in genetically predisposed individuals will lead to priming (sensitization).
- Re-exposure to the same allergen systemically will cause the cross-linking of IgE that are bound to its high-affinity receptors on mast cells and subsequent release of inflammatory mediators including histamine.

Allergy testing



Allergy testing-Characteristic wheal and flare



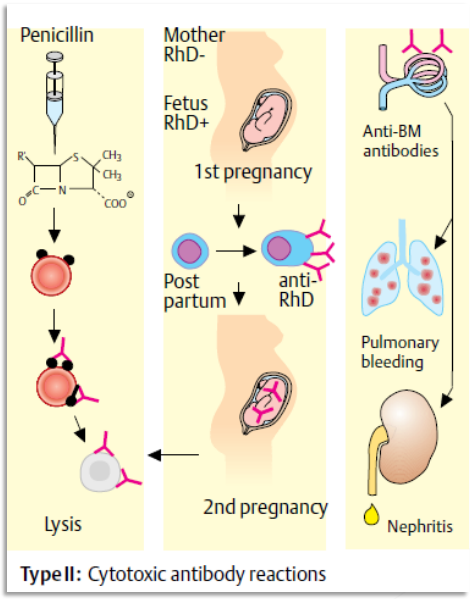
Management of Allergy

- General measures include the identification of the culprit allergen and its avoidance.
- Drug treatment aims at blocking the effect of allergy inflammatory mediators (e.g. antihistamines, β2-adrenergic agonists, epinephrine).
- Topical steroid (anti-inflammatory).
- Sodium cromoglycate (reduces mast cell degranulation).
- Desensitization (immunotherapy). It aims to improve allergy symptoms caused by a specific allergen. Allergen is injected subcutaneously in escalating doses (possible mechanisms include induction of T_H1 response or induction of T_{reg} response that inhibits the polarized T_H2 response.

Ab-mediated HSR (Type II)

- Type II HSRs are initiated by interaction of Abs (IgG or IgM) with cell membranes or extracellular matrix (ECM) components. The Ags can be self or exogenous molecules that are adsorbed to membranes or ECM.
- Tissue damage can occur through: **activation of the complement system**, **ADCC** or **phagocytosis** with the Abs acting as opsonins.
- Abs against cellular or tissue Ags tend to be specific (i.e. affecting the cells or tissues where the Ag is present), whereas the immune complex disease (type III HSR) manifestations reflect the site of immune complex deposition and tend to be systemic.

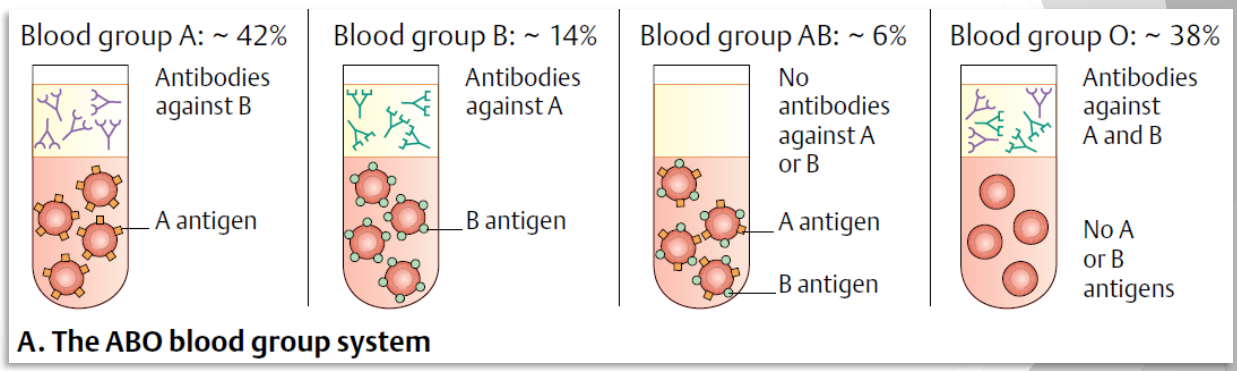
Ab-mediated HSR (Type II)



Ab-mediated HSR (Immune-mediated hemolysis)

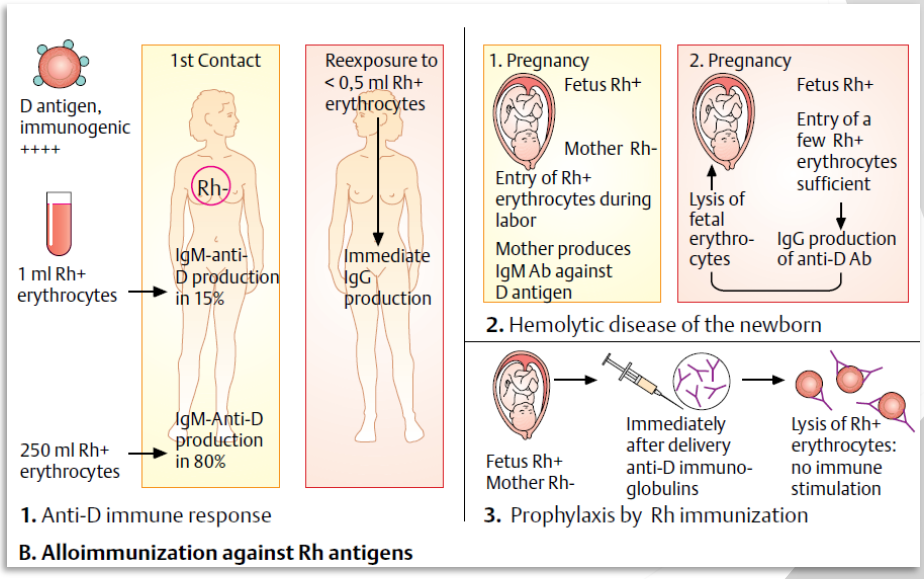
- Antigens of the ABO and Rh (C, D and E) systems are termed "alloantigens", i.e. these Ags might differ from person to person.
- Anti-ABO Abs occur naturally in individuals lacking the A or B Ags and are of the IgM type (strong complement activator). Their natural occurrence is likely due to the ubiquitous presence of identical epitopes in a variety of microbes.
- Anti-Rh Abs arise upon exposure to Rh Ags in individuals lacking these Ags, and are of the IgG type which coat the erythrocytes and recognized by Fc receptors on the splenic and hepatic resident macrophages.

Ab-mediated HSR (Immune-mediated hemolysis)



A. The ABO blood group system

Ab-mediated HSR (Immune-mediated hemolysis)

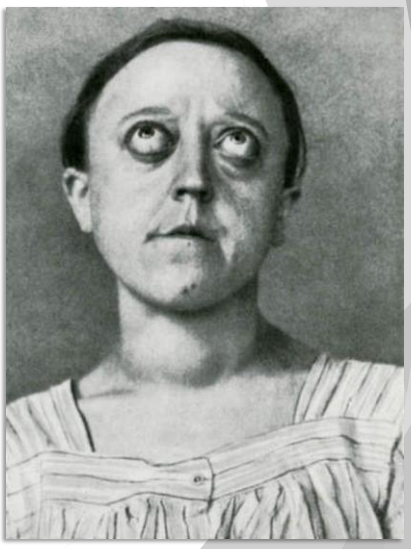


Ab-mediated HSR against solid tissue

- **Goodpasteur's syndrome:** Auto-Abs are synthesized against **type IV collagen present in the basement membranes of the kidneys and lungs**. The tissue damage will be manifested clinically in hematuria, proteinuria and pulmonary hemorrhage. The diagnosis depends on detection of the Ab in the serum (indirect) or in tissue biopsy (direct immunofluorescence test).
- **Pemphigus vulgaris:** A skin disease characterized by bullae. The auto-Abs are directed against **desmogleins of the tight junctions in the skin**.
- **Myasthenia gravis:** An autoimmune disease that is characterised by muscle weakness and fatigue. The name was derived from Greek language and means (myo: muscle, asthenia: weakness) and the Latin language (gravis: serious). Clinically, myasthenia gravis manifests with fluctuating fatigability and weakness affecting a variety of muscle groups (type V).

Ab-mediated HSR affecting cellular function

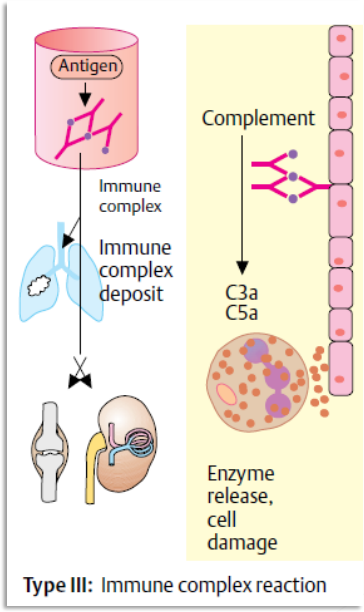
- **Graves disease: (type V)**
  - Auto-Abs specific for TSH receptor mimicking the stimulating effect of the hormone can cause the disease without tissue damage.
- **Wegener's granulomatosis (granulomatosis with polyangiitis):**
  - Vasculitis caused by auto-Abs against proteinase 3 that is present in PMNs (the Abs are termed cytoplasmic anti neutrophil cytoplasmic Abs [c-ANCA]). c-ANCAs activates PMNs and cause degranulation with subsequent damage of endothelial cells.



Immune complex HSR (Type III)

- Immune complexes are lattices of Abs and with its cognate Ags. The physiologic function of immune complex formation is to facilitate the clearance of Ags by phagocytes. However, the presence of large numbers and networks of immune complexes can lead to tissue damage.
- Failure of the immune mechanisms to clear immune complexes due to ongoing excessive production (e.g. chronic antigenemia), will end up in activating the complement system and recruiting leukocytes with ensuing inflammation and tissue damage.
- Immune complex deposition is most likely where there is high blood pressure and turbulence (e.g. glomerular capillaries).
- Deposited immune complexes can be visualized using immunofluorescence which aids in diagnosis.

Immune complex HSR (Type III)



Type III: Immune complex reaction

Immune complex HSR (Type III)

- **Systemic lupus erythematosus (SLE):**

  - The prototypic autoimmune disease characterized by the production of Abs to components of the cell nucleus in association with a diverse array of systemic clinical manifestations.

- **Poststreptococcal glomerulonephritis:**

  - Glomerulonephritis streptococcal Ags with biochemical affinity for glomerular basement membrane, circulating immune complexes, and activation of complement.

Thanks for listening