Clinical immunology

Outline

- Terms and definitions
- Evolution
- Overview of investigations
- Disorders of immune system
  - Immune deficiencies
  - Autoimmunity
  - (Allergy)
  - (Malignancy)
  - (Transplantation medicine)

Terms and definitions

- Complex system of cells and molecules with special roles in defense against infection
- Levels of defence
  - Skin and mucosal surfaces (enzymes, pH, mucus, cilia) – antimicrobial properties, inhibition of microbial adhesion
  - Non-specific (innate) immunity – same type and extent of action in repeated microbe exposure
  - Specific (adaptive, acquired) immunity – improves efficacy in repeated microbe exposure

Mechanisms of innate immunity

- Phagocytic system
  - Neutrophil leucocytes
  - Monocytes
  - Macrophages
- Mediator-releasing cells
  - Basophilic granulocytes
  - Mast cells
  - Eosinophilic granulocytes
- Complement, acute-phase proteins, cytokines (interferons)

Acquired immunity

- Proliferation of Ag-specific B and T cells
  - Response to Ag presentation by APC
  - **„Humoral“** – provided by B-cells – Ig production (extracellular pathogen elimination)
  - **„Cellular“** – provided by T-cells:
    - Provide help to Ab production
    - Destroy intracellular pathogens (Macrophage activation, destruction of virus-infected cells)

Immune system evolution

- Source : Pluripotent stem cell of yolk sac (week 3) to fetal liver (week 5)
- Sites of maturation in primary lymphoid tissue (week 8-11):
  - B-cells: bone marrow
  - T-cells: thymus
- Sites of acquired immune response: secondary lymphatic organs:
  - LN, spleen, MALT

T-cell development

- Thymus seeded by blood-borne T-cell precursors from fetal liver (pro-T cells), evolution of TCRs (through TCRgene rearrangement-random combinations → enormous TCR diversity)
- Upon TCR expression – selection processes start
  - **Positive selection** – interaction of immature thymocytes expressing low levels of TCR with MHC on thymic epithelium (CD4 – HLA II, CD8 – HLA I) – selection of **cells capable to interact with foreign antigens** presented on self MHC
  - **Negative selection** – thymocytes with high TCR expression reacting with self peptides presented by HLA I or II of thymic macrophages induces apoptosis – deletion of **autoreactive cells**
- Migration of T cells to secondary lymphoid organs

B-cell development

- Fetal liver stem cells (wk 7) seed bone marrow
- **Antigen-independent** development (immunoglobulin gene rearrangement processes) reached by wk 14 – mature (virgin) B cell
- **Antigen-dependent** development – after stimulation by Ag through antigen receptor (sIg)
  - Differentiation into memory cells (for particular Ag) and plasma cells (secreteing Ag-specific Ig=antibody)
  - Ig isotypes : M,G,A,D,E

Immunoglobulins

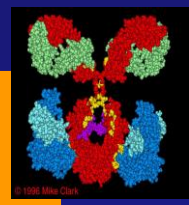
- IgG+M = the only C-fixing Igs, main protection against infection
- IgM-intravascular, IgG – all fluids
- IgA – surface protection (secretions)
- IgE – defense against parasites, mediator of immediate type of allergic reaction
- Maternal IgG cross placenta from wk 12 by birth when reach maternal level

- **Primary Ab response:** native Ag is carried to the draining LN, taken up by specialised cells (FDCs), expressed and presented to virgin B-cells→evolution into plasma cell, production of Ag-specific IgM (low-affinity)
- Some B-cells become memory cells
  - Can switch Ig genes to IgG, A or E production
- **Secondary Ab response** – upon memory B-cell encounters Ab again
  - More cells generated, somatic mutation of Ig genes increases affinity

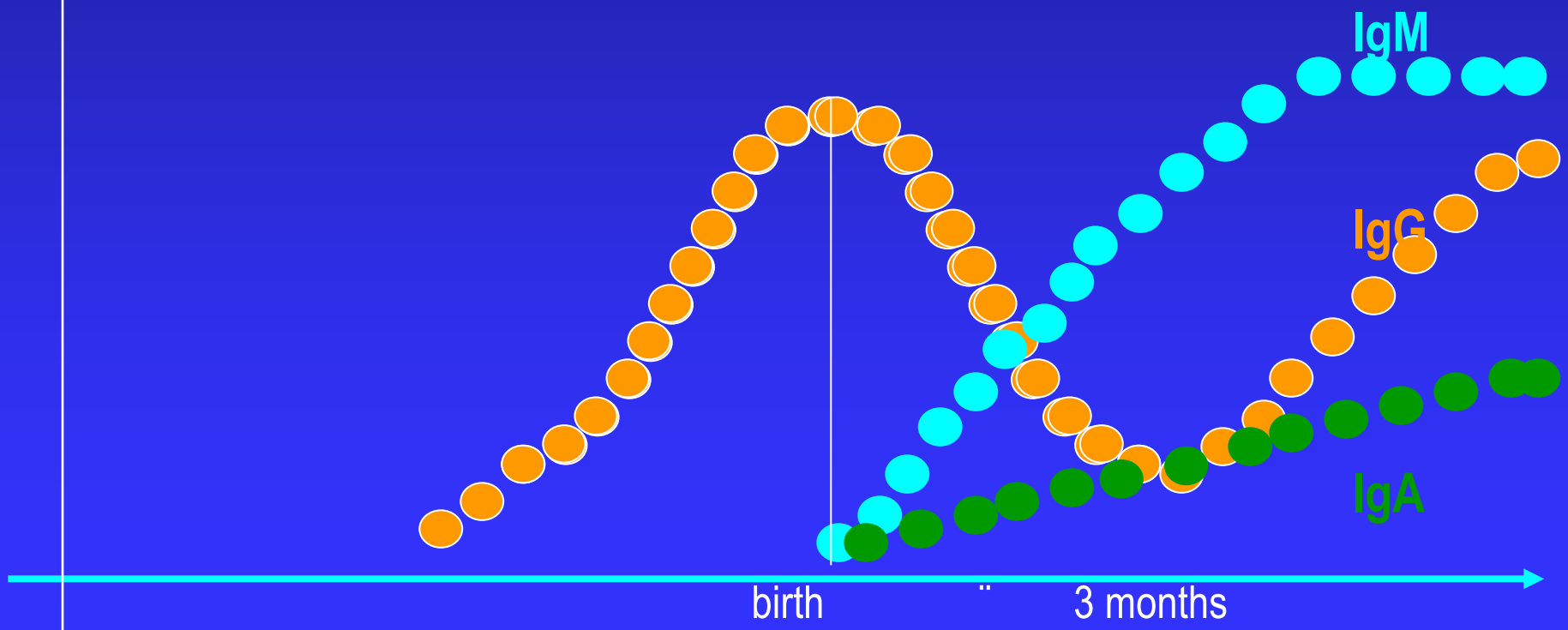
Postnatal lymphopoesis

- **B-cells**
  - Higher in cord blood, do not make full Ig range, start with IgM in response to Ag stimulation from environment (premature have this ability)
  - Total Ig level at minimum around 3-4 mo
  - Ability to produce Ab against protein Ag – from birth, against polysaccharides from 2y (conjugated vaccines e.g.HIB)
  - Newborns susceptible to G- organisms because lack of IgM (=opsonins)-impaired phagocytosis by PMN
  - Mother IgG serve as opsonins for most G+ bacteria, specific IgGs against common viral infetions suffice
  - Premature infants receive less IgG-lower opsonic activity to all types of organisms

Evolution of antibody production



- Fetal Ab = IgG transplacental



Immunopathology

Homeostasis dysregulation

- Immune deficiencies
- Alergies
- Autoimmunity
- Neoplasia
- Graft rejection

Immunodeficiencies

Evaluation of suspected immunodeficiency

- Major cause of recurrent infections: excessive exposure to infectious agents in group settings
- Indications for immunologic evaluation
  - ≥2 systemic or serious bacterial infections
  - ≥3 serious respiratory or bacterial soft tissue infections in 1 year
  - Infections at unusual sites (liver, brain abscess)
  - Infections with unusual pathogens
  - Unusually severe infections with common pathogens

Screening evaluation

- Thorough history
- Physical exam
- Laboratory screening
  - FBC, diff, ESR
  - B-cells: IgA (G,M), isohemagglutinins, Ab to tetanus, diphteria, H.Infl., S.pneumoniae
  - T-cells: Abs L count, Candida intradermal skin rest (or MxII)
  - Phagocytes: Abs N count, respiratory burst assay
  - Complement: CH_{50}

FBC, ESR

- Normal L count: T-cell defects unlikely
- Normal N count: precludes neutropenia, leucocyte adhesion deficiency
- Normal Plt count: excludes Wiscott-Aldrich syndrome
- Normal ESR: chronic bacterial or fungal infection unlikely

Primary deficiencies of acquired immunity: Antibody production defects

Primary defects of antibody production

- Most frequent of the primary ID
- **Clinically:** recurrentinfections with encapsulated bacteria or history of failure to respond to ATB
- Selective IgA deficiency – most common (1/300-1/16000), agammaglobulinemia (1/50000)
- **Genetic defects** recognised for many, not only in B, but also T-cells providing help
- **Therapy:**
  - antibiotics + regular Ig replacement therapy (IVIG)
  - Bone marrow transplantation for CD40 ligand defect and XLP

XLA (Bruton)

- Profound defect in Bcell development, absence of circulating B cells, small to absent tonsils and no palpable LN
- Defective gene (long arm X chr) for tyrosin kinase (Btk), necessary for maturation
- Most affected boys well over initial 6 mo of life, then infections with extracellular pyogenic organisms
- Dg: screening, FACS, prenatal mutation analysis in male fetuses of carrier mothers (chorionic villus)

CVID

- Hypogammaglobulinaemia with phenotypically normal B cells
- Later age at onset of infections
- Equal sex distribution, less severe infections than in XLA
- In most cases no identified molecular defect
- Connection to isolated IgA deficiency
- Serum Ig low, autoAb formation possible, normal or enlarged tonsils and LN, splenomegaly, higher rate of lymphomas

- **Selective IgA deficiency**
  - Genetic basis unknown
  - Respiratory, GI, urogenital infections
  - High incidence of autoimmune diseases, increased malignancies
  - Ab against IgA in 44%(blood rpoducts highly purified)
- **Transient hypogammaglobulinaemia of infancy**
  - Extension of physiologic hypogammaglobulinaemia
- **IgG subclass deficiences**
- **Hyper IgM syndrome**
  - Genetically heterogenious
  - X-linked – T-cell defect of CD40L (inability of T-cells to provide help necessary for switch of Ig isotype), recurrent pyogenic infections from 1 year, small LN and tonsils, normal number of B-cells, often neutropenia, susceptibility to P.carinii
  - X-linked from mutations in gene for NF-kB essential modulator (NEMO deficiency)
  - AR from mutations in the gene for AID, CD40

Primary deficiencies of acquired immunity: T-cell deficiencies

Primary defects of cellular immunity

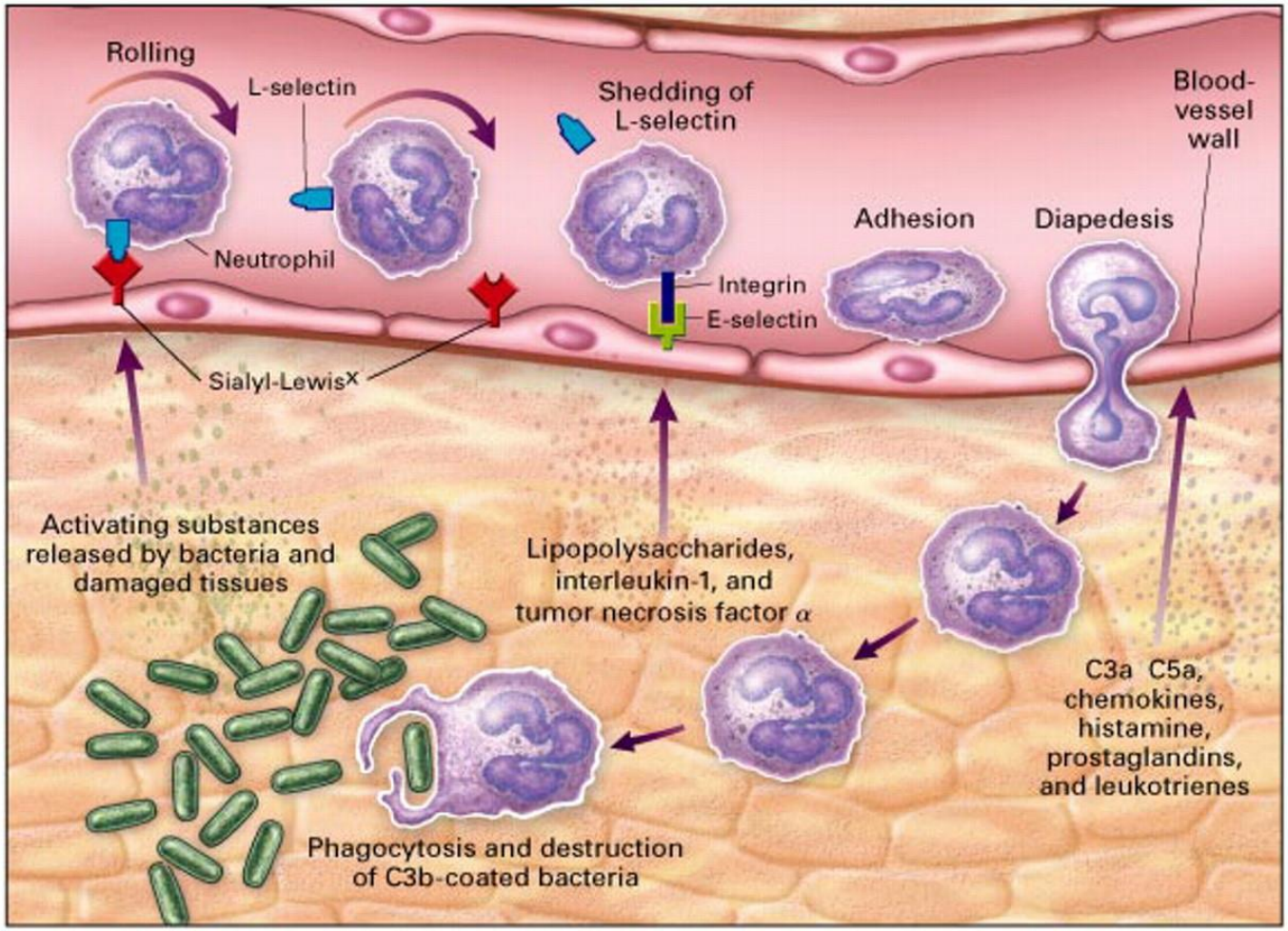
- Generally more severe infections, often fungi, viruses, pneumocystis
- **Thymic hypoplasia (DiGeorge syndrome)**
  - Dysmorphogenesis of the 3rd and 4th pharyngeal pouches in early embryogenesis
  - Parathyroid glands and often other structures (aortic arch, heart, oesophagus, uvula..) also affected
  - Often hypocalcemic seizures in neonate
  - Variable degree of thymic deficiency („partial“ syndrome)
  - Therapy: HLA-identical sibling BMT, thymic tissue transplants
- Defective cytokine production, T-cell activation defects

Primary combined immunodeficiences

- Severe, often opportunistic infections, death in early infancy or childhood unless early BMT provided
- **SCID**
  - Diverse mutations, absence of all adaptive immune functions (X-linked-common cytokine receptor gamma chain 45%, AR – ADA deficiency 15%...)
  - In some – lack of NK cells
  - Small thymus, underdeveloped lymphoid tissues
  - Early presentation with various severe infections with wasting, persistent opportunistic infections (cave BCG), GVHD from maternal T cells or non-irrdiated blood rpoducts
  - Lymphopenia at birth
  - Therapy : pediatric emergency, without BMT death before 1st year
  - Gene therapy in the future

Primary deficiencies of acquired immunity:
Defect of innate immunity

Acute inflammatory response



Phagocyte function disorders

- **Leukocyte adhesion deficiency**
  - LAD1 (integrin CD18), LAD2, AR disorders, 1/10 million, recurrent bacterial and fungal infections, depressed inflammatory response with marked neutrophilia
- **Chédiak-Higashi syndrome**
  - AR disorder, defective degranulation of neutrophils, mild bleeding diathesis, oculocuatneous albinism, peripheral neuropathy, lymphoma-like syndrome
- **Chronic granulomatous disease**
  - Inability of Ne and Mo to kill ingested microbes, accumulation of ingested material, formation of granulomas
  - Defet of the generation of oxygen metabolites
  - Incidence 4-5/1 million, X-linked in 2/3, 1/3 AR
  - Recurrent/unusual lymphadenitis, multiple osteomyelitis, hepatic abscesses, unusual Staph infections
  - Onset from early infancy to adulthood
  - NBT test, DHR test (flow cytometry)
  - Therapy: supportive care + IFNgamma followed by BMT,

Complement disorders

- Primary deficiences – of all 11 components of classical membrane attack pathway possible
  - C1q (and other components) deficiency – SLE-like syndrome
  - Recurrent Neisseria infections typical
- Deficiences of C control proteins
  - Properdin def – predisposition to meningococcal infection
  - Hereditary angioedema – abnormal synthesis of C1 inhibitor (5-30%), acquired form possible

Leucopenia

- Note developmental changes

Neutropenia: acute, chronic, drug-induced

  - Infections primarily from endogeneous flora and nosocomials. Fever, soft tissue, mucous memb and skin, respiratory and GI tract, most comonly Staph, G- bact
  - Therapy: rhG-CSF, ATB

- *Immune-mediated*
  - Circulating antineutrophil Ab
  - ANN (alloimmune neonatal) – transfer ofmaternal Ab, isolated, ANI (infancy)
- *Ineffective myelopoiesis* (vit B12, folic acid def., malabsorption...)
- *Intrinsic disorders of myeloid stem cells*
    - Cyclic neutropenia- AR, regulatory abnormality
    - Severe congenital neutropenia – Kostmanndisease
    - Schwachman-Diamond disese – AR, GI disorder + neutropenia, by 4 mo, chondrodysplasia
    - GSD Ib(vonGierke)

Lymphopenia

- 65% of CD3 (T cells) are CD4 helper T lymphocytes
- Often no specific symptoms
- Inherited causes
- Acquired: AIDS (destruction of infected CD4), other infections, therapy side effects, immune-mediated