Immunodeficiency
Selected Topics in Clinical Immunology

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Defects in MATURATION and/or ACTIVATION of the immune system

Immunodeficiency

Physiological
- Infancy
- Pregnancy
- Age

Primary
- Adaptive
- Innate
- Combined

Secondary
- Chemical
- Physical
- Malnutrition
- Chronic infections
Definition of Primary Immunodeficiency

- INTRINSIC defects in MATURATION and/or ACTIVATION of the immune system
- Opposed to secondary immunodeficiency which are caused by EXTRINSIC stimuli (e.g. medication, chronic infections, malnutrition)
Primary Immunodeficiency: May Affect the Innate and/or the Adaptive Immunity

Darnoff et al. 2004 Nat Rev Cancer
Classification of Primary Immunodeficiency

Specific
- Predominantly Antibody Deficiency
- Combined Immunodeficiency
- Well-defined Syndromes of Immunodeficiency
- Autoinflammatory Disorders
- Immune Dysregulation

Non-specific
- Congenital Defects of Phagocyte Numbers, Function or Both
- Complement Deficiency
- Innate Immunity
Distribution of PID Categories in Switzerland

Marschall et al. 2015 Clin Exp Immunol
Think Zebra

Immune Deficiency Foundation, USA
10 Warning Signs of Primary Immunodeficiency

- Four or more new ear infections within 1 year for children, two or more in 1 year for adults
- Two or more serious sinus infections within 1 year
- Two or more bouts of pneumonia within 1 year for children, and recurrent pneumonia for adults
- Chronic diarrhea with weight loss, and failure to grow normally or gain weight in children
- Recurrent viral infections
- Persistent thrush or fungal infection on skin or elsewhere
- Recurrent deep skin or organ abscesses
- Need for intravenous antibiotics to clear infections
- Two or more deep-seated infections including septicemia
- A family history of primary immunodeficiency

Adapted from Jeffrey Modell Foundation
http://www.info4pi.org/aboutPI/pdf/Adult10WarningSigns-FINAL.pdf
http://www.info4pi.org/aboutPI/pdf/General10WarningSignsFINAL.pdf.
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Common Variable Immunodeficiency: Clinical Symptoms

- Increased susceptibility to bacterial, viral and fungal infection (bronchitis, pneumonia, ear or skin infections)
- Chronic sinusitis
- Bronchiectasis
- Granulomas
- Fatigues
- Disorders of the digestive tract, diarrhea
- Spleen enlargement (splenomegaly)
- Unexplained polyclonal lymphoproliferation (> lymphadenopathy)
- Autoimmune manifestation (e.g. autoimmune haemolytic anaemia, autoimmune thrombocytopenia)
Common Variable Immunodeficiency: Defects in B Cell Development and Maturation

- low number of B cells
- Paucity of unswitched or switched B cells
- Increased CD21/CD38low B cells
- Increased transitional B cells
- Deficiency in plasma blast

Hypogammaglobulinaemia: decreased IgG and IgA with or without low IgM
Common Variable Immunodeficiency: Diagnosis

- Immunophenotyping of blood B cell subpopulations by flow cytometry
- Determination of levels of serum immunoglobulin
- Determination whether there is a lack of functional antibodies
B cell Subtypes

- **naïve**
  - CD21
  - CD38^{dim}
  - CD19
  - IgD

- **transitional**
  - CD19
  - CD38^{high}

- **CD21/CD38^{low}**
  - CD19
  - CD38^{low}

- **non-switched memory**
  - CD19
  - CD38^{dim}
  - CD27
  - IgD

- **switched memory**
  - CD19
  - CD38^{dim}
  - CD27

- **plasmablast**
  - CD19
  - CD38^{high}
  - CD27
Determination of B cell Subtypes by Flow Cytometry

- **SSC**
  - CD45 APC-H7

- **CD3 V500**
  - CD19 BV

- **IgD FITC**
  - CD27 PE
  - CD21 PE-Cy7
  - CD38 PerCP-Cy5.5
  - CD24 APC

- **Naïve**
  - CD21low

- **Switched**
  - Plasma Blast

- **Transitional**
  - CD21 PE-Cy7
  - CD27 PE

- **Plasma Blast**
  - CD38 PerCP-Cy5.5

- **Non-switched**
  - Transitional
  - Switched
Examples of CVID

Healthy

Low non-switched

Low switched

Healthy

High CD21/CD38<sub>low</sub>

CD21 PE-Cy7

CD38 PerCP-Cy5.5

B cells
T cell-dependent B cell Activation and Isotype Switching

- ICOS induced on activated T cells
- Enhances T-cell responses, T-cell-B-cell cooperation
- Induces IL-10 (Th-1 differentiation inhibitor) and IL-17
- Augments isotype class-switching in B cells

Park et al. 2008 The Lancet
Determination of T cells Activity by Lymphocyte Transformation Test (LTT)

Activation:
dTT
PWM
Anti-CD3/Anti-CD28

Result:
Stimulation Index
(cpm stimulated/cpm unstimulated)

count radioactivity
harvest cells
T cell Activity in CVID Population

Impaired T cell Response to Recall Antigen
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Defects in T cell Development: Autoimmune Lymphoproliferative Syndrome (ALPS)

Defective T cell homeostasis due to mutations in Caspase-8, Caspase-10, CD95L or CD95 results in nonfunctional death-inducing signaling complex (DISC)

Impaired Apoptosis

Lymphoproliferation
Autoimmunity
Hypergammaglopolinaemia

Cunningham et al. 2005 Nat Rev Immunol
Normal Distribution of $\alpha/\beta$ and $\gamma/\delta$ T cells
Abnormal Distribution of $\alpha/\beta$ and $\gamma/\delta$ T cells
Case 1: Malignancy or ALPS?

- 18-months of age, female
- Lymphadenopathy, Splenomegaly
- White blood count 12’500 cells/µl (normal 5’000-10’000 cells/µl)
- Lymphocyte count 9175 cell/µl (normal 3’000 cells/µl)
- B cells: 29% of lymphocytes (normal range 5-15%)
- IgG: 4’000mg/dl (normal 520-1’500), IgM 400mg/dl (normal 40-200), IgA 1’660mg/dl (normal 27-169)
- T cells: 65% of lymphocytes (normal range 61-84%)
- CD4positive T cells: 14% of T cells
- CD8positive T cells:18% of T cells
- ?????????
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Severe Combined Immunodeficiency (SCID)

$T^-B^+NK^-$ SCID: X-linked-recessive SCID (Common $\gamma$-chain deficiency)

$T^-B^+NK^-$ SCID: Jak3-deficiency

$T^-B^+NK^+$ SCID: IL-7R$\alpha$-deficiency

Rochman et al. 2009 Nat Rev Immunol
Severe Combined Immunodeficiency (SCID)

**T⁻B⁺NK⁻ SCID:** X-linked-recessive SCID (Common $\gamma$-chain deficiency)

**T⁻B⁺NK⁻ SCID:** Jak3-deficiency

**T⁻B⁺NK⁺ SCID:** IL-7R$\alpha$-deficiency

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**Cytokine produced by:**

- **IL-2:** T cells and DCs
- **IL-4:** T cells, NK cells, eosinophils and mast cells
- **IL-7:** stromal cells, epithelial cells and fibroblasts
- **IL-9:** T cells
- **IL-15:** monocytes, DCs and epithelial cells
- **IL-21:** CD4$^+$ T cells and NK cells
- **TSLP:** stromal cells, fibroblasts, mast cells and basophils

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**Receptor expressed by:**

- **T cells, B cells, NK cells, mast cells and basophils**
- **T cells, B cells, NK cells, mast cells and basophils**
- **T cells, pre-B cells and DCs**
- **T cells, mast cells, epithelial cells and eosinophils**
- **T cells and NK cells**
- **T cells, B cells, NK cells and DCs**
- **T cells, B cells, DCs, NK cells and mast cells**

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- **Non-functional B cells**
- **No T cells**
- **No NK cells**
- **Non-functional B cells**

Rochman et al. 2009 Nat Rev Immunol
Severe Combined Immunodeficiency (SCID)

- **T- B⁺NK⁻ SCID**: X-linked-recessive SCID (Common γ-chain deficiency)
- **T- B⁺NK⁻ SCID**: Jak3-deficiency
- **T- B⁺NK⁺ SCID**: IL-7Rα-deficiency

![Cytokine diagram]

Rochman et al. 2009 Nat Rev Immunol
Severe Combined Immunodeficiency (SCID)

**T-B⁺NK⁻ SCID:** X-linked-recessive SCID (Common $\gamma$-chain deficiency)

**T-B⁺NK⁻ SCID:** Jak3-deficiency

**T-B⁺NK⁺ SCID:** IL-7R$_{\alpha}$-deficiency

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Rochman et al. 2009 Nat Rev Immunol
Severe Combined Immunodeficiency (SCID)

T<sup>-</sup>B<sup>-</sup>NK<sup>+</sup> SCID: RAG-deficiency

RAG: Recombination-activating gene 1 & 2
Encode recombination signal sequences (RSSs)
Catalyze V(D)J-rearrangement

Nemazee et al. 2006 Nat Rev immunol
Severe Combined Immunodeficiency (SCID)

**T⁻B⁻NK⁻ SCID: Adenosine-deaminase (ADA) deficiency**

- **If in Excess**: Inhibition of ribonucleotide reductase

Diagram showing the metabolic pathway involving the enzymes ribonucleotide reductase, adenosine deaminase, and the excretion of uric acid.
Severe Combined Immunodeficiency (SCID)

T⁻B⁻NK⁻ SCID: Adenosine-deaminase (ADA) deficiency

If in Excess> Inhibition of ribonucleotide reductase

Case Studies in Immunology 7th Edition

Excretion
Case 2: X-linked recessive SCID, Jak3-deficiency, RAG-deficiency or ADA-deficiency?

• 3 months of age, male:
  – recurrent infection
  – persistent cough >pneumonia
  – not gaining weight
  – Suffers from Candida ablicans in the mouth

• older sister, father, mother > no symptoms

• Hospitalization:
  – Very small tonsils
  – Detection of Pseudomonas aeruginosa in nasal fluid
  – White blood count 4’800 cells/µl (normal 5’000-10’000 cells/µl)
  – Lymphocyte count 760 cell/µl (normal 3’000 cells/µl)
  – IgG: 30mg/dl (normal 520-1’500), IgM 12mg/dl (normal 40-200), IgA non-detectable
  – Functional analysis: lymphocytes did not react upon stimulation (phytohemagglutinin, vaccine antigens)
  – 95% of lymphocytes were B cells (normal range 5-15%)
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Chronic Granulomatous Disease (CGD)

Defects in NADPH-Oxidase-Complex NOX2: no formation of superoxide

Lambeth et al. 2004, Nat Rev Immunol

25% (autosomal recessive)
70% (X-linked)
5% (autosomal recessive)
• Autosomal recessive genetic defect in CD18
• CD18: common $\beta$-chain of integrin receptors: LFA-1, Mac-1 and p150,95
• Defect in adhesion, chemotaxis and complement binding

Quinn et al. 2014, Humana Press
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Complement Pathways

- Surfaces
- Immune complexes
- Polysaccharides

Opsonization
C3a, C5a
Chemotaxis
Inflammation

Opsonization
Lysis

Adapted from medscape.com
Consequences of Complement Deficiencies

Deficiency in:

- Early C Components (C1q, C1r/s, C2, C4): failure of clearance of immune complexes, apoptotic cells > autoimmune manifestation
- MBL: increased risk of infection with encapsulated bacteria
- C3: defect in opsonization, deficient chemotaxis of leukocytes, decreased MAC formation > increased risk of infection with encapsulated bacteria
- MAC: increased risk of infection, especially Meningococcal meningitis
Hereditary Angioedema (HAE): Deficiency in C1INH

C1q inhibitor C1INH

C1q → C1r → C1s → C4b

C2b

C2 kinin

bradykinin

Vasodilation
Increased permeability

Injury blood vessels

Clotting system

Classical Pathway

Injury blood vessels

Plasmin

University Institute of Clinical Chemistry M. Fux
Hereditary Angioedema (HAE): Deficiency in C1INH

- C4, C2 decreased, late C components normal
- No increased susceptibility to infections
- Swelling of the skin, intestine and airway
- Edema fluid is free of cellular component (≠ anaphylactic edema)
- Normally no itching and hives (≠ allergy)
Alternative Pathway: Factor I Deficiency

- C3 decreased, nonproduction of iC3b > defective opsonization
- Late C components decreased
- Sustained itching and hives
- Increased susceptibility to infections, especially Neisseria
Case 3: HAE or Factor I Deficiency?

- 25-year old man
- Hives after drinking alcohol or taking a shower
- Hematocrit, white cell count and platelet count normal
- Red blood cells >positive agglutination reaction with anti-C3 Ab
- IgG, IgM and IgA serum levels normal
- Normal response to tetanus toxoid
- Serum levels of C3 27mg/dl (normal 97-104mg/dl) of this 8mg/ml was C3 and 19mg/ml was C3b
- His serum failed to kill Salmonella enterica, even after addition of C3
- Synthesis of C3 was normal but C3 was being broken down 4-times faster than normal
Thank You