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
Primary Immunodeficiency: May Affect the Innate and/or the Adaptive Immune System

Darnoff et al. 2004 Nat Rev Cancer
Diagnostic Delay in PID

Reda et al. 2013 Allergy Asthma Immunol Res
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
### Table 5: Frequency of warning signs among patients with PID compared with non PID

<table>
<thead>
<tr>
<th>Warning signs</th>
<th>Non PID n (%)</th>
<th>PID n (%)</th>
<th>Combined T- and B-cell immunodeficiencies n (%)</th>
<th>Predominantly antibody deficiency n (%)</th>
<th>Other well defined immunodeficiency syndromes n (%)</th>
<th>Congenital defects of phagocyte number, function or both n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4 new ear infections within 1 yr</td>
<td>0 (0)</td>
<td>19 (21)*</td>
<td>5 (19)*</td>
<td>9 (33)*</td>
<td>4 (17)*</td>
<td>1 (7)</td>
</tr>
<tr>
<td>≥2 months on antibiotics with little effect</td>
<td>0 (0)</td>
<td>36 (39)*</td>
<td>13 (50)*</td>
<td>10 (37)*</td>
<td>6 (26)*</td>
<td>7 (47)*</td>
</tr>
<tr>
<td>≥2 pneumonias within 1 yr</td>
<td>41 (37)</td>
<td>52 (56)*</td>
<td>11 (42)</td>
<td>19 (70)*</td>
<td>13 (56)</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Failure of infant to gain weight</td>
<td>37 (33)</td>
<td>54 (59)*</td>
<td>17 (65)*</td>
<td>17 (63)*</td>
<td>12 (52)</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Recurrent deep skin or organ abscesses</td>
<td>0 (0)</td>
<td>26 (28)*</td>
<td>4 (15)*</td>
<td>3 (11)*</td>
<td>6 (26)*</td>
<td>13 (87)*</td>
</tr>
<tr>
<td>Persistent oral thrush or fungal infection of skin</td>
<td>1 (1)</td>
<td>19 (21)*</td>
<td>16 (61)*</td>
<td>0</td>
<td>0</td>
<td>3 (20)*</td>
</tr>
<tr>
<td>Need for intravenous antibiotics to clear infections</td>
<td>59 (53)</td>
<td>85 (92)*</td>
<td>26 (100)*</td>
<td>25 (93)*</td>
<td>20 (87)*</td>
<td>13 (87)*</td>
</tr>
<tr>
<td>≥2 deep seated infections</td>
<td>1 (1)</td>
<td>20 (22)*</td>
<td>8 (31)*</td>
<td>0</td>
<td>2 (9)</td>
<td>10 (67)*</td>
</tr>
<tr>
<td>Family history of PID</td>
<td>1 (1)</td>
<td>21 (23)*</td>
<td>4 (15)*</td>
<td>3 (11)*</td>
<td>8 (35)*</td>
<td>6 (40)*</td>
</tr>
</tbody>
</table>

\[X^2\] analysis was used for comparison between children with PID and non PID. 
*P≤0.01, "P<0.05.

Reda et al. 2013 Allergy Asthma Immunol Res
Distribution of PID Categories in Switzerland

Marschall et al. 2015 Clin Exp Immunol
Classification of Primary Immunodeficiency

Specific
- Predominantly Antibody Deficiency
- Combined Immunodeficiency

Non-specific
- Well-defined Syndromes of Immunodeficiency
- Autoinflammatory Disorders
- Immune Dysregulation
- Congenital Defects of Phagocyte Numbers, Function or Both
- Complement Deficiency
- Innate Immunity

Specific
- Combined Immunodeficiency

Non-specific
Defects in B Cell Development and Maturation: Common Variable Immunodeficiency

- Mainly a polygenetic disorder, only 20% monogenic cause (TACI, BAFF-R)
- Hypogammaglobulinaemia: decreased IgG and IgA with or without low IgM
- Increased susceptibility to infection
- Development of chronic infections (>bronchiectasis)
- Autoimmune manifestation (e.g. autoimmune haemolytic anaemia, autoimmune thrombocytopenia)
- Unexplained polyclonal lymphoproliferation (> lymphadenopathy)

- Increased transitional B cells
- Low number of B cells
- Paucity of unswitched or switched B cells
- Deficiency in plasma blast
- Increased CD21/CD38low B cells
Common Variable Immunodeficiency: Diagnosis

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

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

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

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

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

- **switched memory**
  - CD19
  - IgD
  - CD27
  - CD24

- **plasmablast**
  - CD19
  - IgD
  - CD27
  - CD38^{high}
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
- Naïve B cells
- CD21low
- Plasma Blast
- Switched Memory B cells
- Transitional B cells
- Non-switched
Examples of CVID

Healthy

Low non-switched

Low switched

Healthy

High CD21/CD38\textsuperscript{low}

CD21 PE-Cy7

CD27 PE

CD21 PE-Cy7

CD21 PE-Cy7

CD38 PerCP-Cy5.5

CD38 PerCP-Cy5.5

B cells
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Defects in Neutrophil DEVELOPMENT
Severe Congenital Neutropenia (SCN)

- Block at the promyelocyte-myelocyte stage
- Marked neutropenia: Less than $0.5 \times 10^9$ cells/L (normal range 2.5-7.5x$10^9$ cells/L)
- Recurrent, severe bacterial infections
- Several genetic defects identified (ELA2, HAX1 etc.)
Defects in Neutrophil DEVELOPMENT
Specific Granule Deficiency (SGD)

- Absence of granule proteins of specific and gelatinase granules (e.g. lactoferrin and defensins)
- Atypical bilobed nuclei
- Stop of maturation beyond promyelocyte
- Mutations in myeloid-specific transcription factor C/EBPε

Serwas et al. 2018 Front Immunol
Defects in Neutrophil FUNCTION
Chronic Granulomatous Disease (CGD)

Inactive NADPH-Oxidase

Cellular activation
Agonsit or phagocytosis

Components form complex

Active NADP-Oxidase

Lambeth et al. 2004, Nat Rev Immunol
Defects in Neutrophil FUNCTION
Chronic Granulomatous Disease (CGD)

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

Lambeth et al. 2004, Nat Rev Immunol
Defects in Neutrophil FUNCTION
Chronic Granulomatous Disease (CGD)

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

- Microbicidal mechanisms are defect
- Sustained activation of CD4+ T cells
- Inflammation
- Formation of Granulomas
Defects in Neutrophil FUNCTION: Leukocyte Adhesion Deficiency Type I

- Autosomal recessive genetic defect in CD18
- CD18: common β-chain of integrin receptors: LFA-1, Mac-1 (CR3) and p150,95 (CR4)
- Defect in adhesion, chemotaxis and complement binding

Quinn et al. 2014, Humana Press
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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
Hypergammaglobulinaemia
Abnormal Distribution of $\alpha/\beta$ and $\gamma/\delta$ T cells
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Specific

Non-specific
Primary Defects in T cells with or without Defects in B and/or NK cells
Severe Combined Immunodeficiency (SCID)

Several Categories (Selection):
– Impaired lymphocyte survival:
  • adenosine deaminase (ADA) deficiency $\rightarrow$ T-B-NK-
– Defects in cytokine-mediated signalling:
  • X-linked (common $\gamma$-chain deficiency), Jak3-deficiency, IL-7R$\alpha$ deficiency $\rightarrow$ T-B$^+$NK$^-$ or T-B$^+$NK$^+$
– Defects in V(D)J recombination process:
  • RAG deficiency T-B-NK$^+$
Severe Combined Immunodeficiency (SCID)

T\(^{-}\)B\(^{-}\)NK\(^{-}\) SCID: Adenosine-deaminase (ADA) deficiency

- If in excess
  - Inhibition of ribonucleotide reductase
  - Inhibition of DNA synthesis
  - Apoptosis

- Excretion

Healthy

Absence of Thymus

Case Studies in Immunology 7\(^{th}\) Edition

University Institute of Clinical Chemistry M. Fux
Severe Combined Immunodeficiency (SCID)
Defects in cytokine-mediated signaling

\[ T^-B^+NK^- \text{ SCID: } \textit{X}-\text{linked-recessive SCID (Common } \gamma\text{-chain deficiency)} \]
\[ T^-B^+NK^- \text{ SCID: } \textit{Jak3}-\text{deficiency} \]

Rochman et al. 2009 Nat Rev Immunol

- No T cells
- No NK cells
- Non-functional B cells
- Non-functional B cells
Severe Combined Immunodeficiency (SCID)
Defects in cytokine-mediated signaling

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

Rochman et al. 2009 Nat Rev Immunol
Severe Combined Immunodeficiency (SCID)
Defects in V(D)J recombination process

$T^+B^+NK^+$ 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
Primary Defects in T cells with or without Defects in B and/or NK cells
Severe Combined Immunodeficiency (SCID)

Newborn Screening

Roshini et al. 2013 AACC
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Specific
- Non-specific
Hereditary Angioedema (HAE): Deficiency in C1INH

- C1q inhibitor C1INH
- C1q
- C1r → C1s
- C4 → C4b
- C2 → C2b → C2 kinin
- kallikrein → kininogen → bradykinin
- Vasoactive peptide
- Plasmin
- Factor XII

- Cleavage
- Binding
- Products
- Functions

Injury blood vessels
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
Thank You
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
• ?????
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%)
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 total 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