Primary Immune Deficiency: Overview

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Immune System: Overview

- **Innate immunity:**
  - Microbe with barriers
  - Epithelial barriers
  - Phagocytes
  - Complement
  - NK cells

- **Adaptive immunity:**
  - B lymphocytes
  - T lymphocytes
  - Antibodies
  - Effector T cells

**Time after infection:**
- Hours: 0, 6, 12
- Days: 1, 3, 5

*Courtesy: Abbas and Litchman; Basic Immunology*
Adaptive Immunity

Humoral immunity:
- Microbe: Extracellular microbes
- Responding lymphocytes: B lymphocyte
- Effector mechanism: Secreted antibody
- Functions: Block infections and eliminate extracellular microbes

Cell-mediated immunity:
- Microbe: Phagocytosed microbes in macrophage
- Responding lymphocytes: Helper T lymphocyte
- Effector mechanism: Activated macrophage
- Functions: Eliminate phagocytosed microbes

Intracellular microbes (e.g., viruses) replicating within infected cell
- Responding lymphocytes: Cytotoxic T lymphocyte
- Effector mechanism: Killed infected cell
- Functions: Kill infected cells and eliminate reservoirs of infection
Complement

**Complement Cascade and Function**

C1 binds to an antigen-antibody complex on an invading pathogen, causing complement components C2 and C4 to split in two.

C3 convertase splits in two. One of the fragments from C3 joins C3 convertase to form C5 convertase.

C3a attracts phagocytes to infection site.

C3b binds to the surface of the pathogen.

C5 convertase splits C5 in two.

A fragment from C5 joins C6, C7, C8, and C9 to form the membrane attack complex, which makes a hole in the pathogen's plasma membrane. Water rushes into the hyperosmotic cytoplasm, causing the pathogen to lyse.
Primary Immunodeficiencies: The Big Picture for Lymphocytes

PID Overview

- SCID
- AT
- X-linked SCID (cytokine γ chain)
- DiGeorge syndrome
- WAS
- MHC Class II deficiency

Diagram illustrates the development of lymphocytes from bone marrow to thymus, highlighting various immunodeficiencies and their respective defects in immune system components.
PID Overview

- Severe Combined Immune Deficiency (SCID)
- X-Linked Agammaglobulinemia (XLA)
- Wiskott-Aldrich Syndrome (WAS)
- Common Variable Immune Deficiency (CVID)
- Complement Deficiency
- Selective IgA deficiency
CASE 1

- 3 month old male hospitalized with pneumonia, failure to thrive
- No lymph nodes palpated
- CBC w/diff showed WBC 3.5, nl Hgb and plt counts
- Total lymphocyte 500/ microl
SCID

- 1% T-cells, 1% B-cells, 90% NK cells
- Gene testing shows mutation in RAG1 gene
- SCID 1 in 58,000 births
- Numerous gene defects cause dysfunction in T cells with varying B and NK cells
# SCID Gene Defects

<table>
<thead>
<tr>
<th>T-B+NK- SCID</th>
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<tbody>
<tr>
<td>X-linked SCID, common gamma chain (gamma-c)</td>
<td>IL2RG</td>
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<tr>
<td>Janus kinase 3</td>
<td>JAK3</td>
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<thead>
<tr>
<th>T-B+NK+ SCID</th>
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<tbody>
<tr>
<td>Interleukin-7 receptor alpha chain (CD127)</td>
<td>IL7RA</td>
</tr>
<tr>
<td>Actin-regulating protein coronin 1A (CORO1A)</td>
<td>CORO1A</td>
</tr>
<tr>
<td>CD3 chain components</td>
<td></td>
</tr>
<tr>
<td>CD3 delta</td>
<td>CD3D</td>
</tr>
<tr>
<td>CD3 epsilon</td>
<td>CD3E</td>
</tr>
<tr>
<td>CD3 zeta</td>
<td>CD3Z</td>
</tr>
<tr>
<td>CD45</td>
<td>PTPRC</td>
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<th>T-B-NK+ SCID</th>
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<tr>
<td>Recombinase-activating genes 1 and 2</td>
<td>RAG1, RAG2</td>
</tr>
<tr>
<td>Artemis</td>
<td>DCLRE1C</td>
</tr>
<tr>
<td>DNA protein kinase catalytic subunit (DNA-PKcs)</td>
<td>PRKDC</td>
</tr>
<tr>
<td>DNA ligase IV</td>
<td>LIG4</td>
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<tr>
<td>Cernunos/XRCC4-like factor (XLF)</td>
<td>NHEJ1</td>
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<th>T-B-NK- SCID</th>
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<tr>
<td>Adenosine deaminase</td>
<td>ADA</td>
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<tr>
<td>Reticular dysgenesis</td>
<td>AK2</td>
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</tbody>
</table>
SCID – Clinical

- Recurrent severe infections
- Chronic diarrhea
- Failure to thrive
- Thrush
- No discernable lymph nodes
- MMR/Varicella may be fatal
SCID - Diagnoses

- Very low lymphocyte counts (<2000), especially T cells
- Hypogammaglobulinemia often found but not required
- Genetic testing
SCID - Treatment

- Hematopoietic stem cell transplant may be curative if given early enough
- HCT given in first 3.5 months increased survival compared to given after (94% vs 70%)
- 5 year survival if given in first 3.5 months 94%
- Gene therapy for X-linked and ADA promising
Case 2

- 12 month old male recurrent otitis
- Chronic high fevers
- Pseudomonas cellulitis
- CBC shows total lymphocytes 600/µl
XLA

- Mutation in *BTK* gene, named after Colonel Ogden Bruton, described in 1952 as X-linked
- 1 in 190,000 male births
- Bruton Tyrosine Kinase is signal transduction molecule, promotes pre-B cell expansion
XLA - Clinical

- Recurrent bacterial infections, otitis, pneumonia, cellulitis
- Sepsis
- Recurrent enteroviral infections
- 50% develop symptoms by first year of age
- Maternal antibodies protect for the first few months of life
- Absence of tonsils (B-cell rich) is hallmark
XLA - Diagnosis

- Reduction in CD19+ B cells and all classes of antibodies (IgG/IgA/IgM)
- Deficient antibodies to all vaccines
- Gene defect in $BTK$
XLA - Treatment

- IV or SC replacement of IgG (IgM and IgA replacement not available)
- Substantial reduction in infections and hospitalizations
- Chronic antibiotics
- Very good life expectancy
Case 3

- 10 month old male with disseminated Neisseria infection
- 2 months prior had episode of Strep pneumonia
- Normal CBC w/diff
- Low CH50
### Complement Deficiencies and Disease

<table>
<thead>
<tr>
<th>Pathway/Component</th>
<th>Disease</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Factors B or D</td>
<td>Susceptibility to pyogenic (pus-forming) bacterial infections</td>
<td>Lack of sufficient opsonization of bacteria</td>
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<tr>
<td>C3</td>
<td>Susceptibility to bacterial infections</td>
<td>Lack of opsonization and inability to utilize the membrane attack pathway</td>
</tr>
<tr>
<td>C5, C6, C7 C8, or C9</td>
<td>Susceptibility to Gram-negative infections</td>
<td>Inability to attack the outer membrane of Gram-negative bacteria</td>
</tr>
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</table>
Complement - Clinical

- C1 – SLE
- C4 – SLE
- C2 – pyogenic infections with encapsulated bacteria
- C3 – severe recurrent infections with encapsulated bacteria shortly after birth
- C5-C9 – recurrent Neisseria infections
Complement - Diagnosis

- CH50 – Total hemolytic component (represent C1-C9)
- If low, measure specific components
- Recurrent pneumocococcus, measure C3
- Recurrent Neisseria, measure C5-C9
  - C6 African American
  - C9 Asian
  - Autosomal recessive
Complement - Alternative

- Very rare
- Properdin
  - Neisseria Meningitis
  - High mortality
- Factor D
  - <5 cases
  - Meningococcal sepsis
- Factor B
  - 1 case, severe pneumococcus
Mannose Binding Lectin (MBL)

- MBL < 500 ng/ml
- Does not correlate with disorder
- Low levels in healthy individuals
- Pneumococcal disease
- Treat infections
Complement - Treatment

- Pneumococcus and Meningocococcus vaccines
- In theory, plasma infusions
  - Rarely done
  - Risk of antibody formation to missing component
  - Risk of bloodborne illness
  - Need for frequent infusions
Case 4

- 8 year old girl 3 years of sinusitis, 3 times a year
  - Pneumococculus cultured on several occasions
- Episode of Giardia when she was younger
- Type 1 Diabetes
IgA Deficiency

• 1 in 600 people, low IgA or deficient
• Most people asymptomatic and no workup is needed
• Primary found in respiratory and gastrointestinal mucosa
• Patients that are symptomatic, recurrent sinopulmonary infections
• Precise defect and inheritance pattern unknown
IgA Deficiency

- Not a lot of GI infections because IgM, but Giardia more common
- 20-30% have autoimmune disorders
  - Graves
  - Type 1 Diabetes
  - Rheumatoid Arthritis
  - ITP
- Thought to be from compromise of negative selection
IgA Deficiency - Diagnosis

- Low or absent serum IgA, with normal IgG
- Recurrent sinopulmonary infections
- Impaired antibody response: pneumococcus, measles, Hib, diphtheria, etc.
IgA Deficiency - Management

- Treat infections – if frequent, prophylactic antibiotics
- IVIG
  - Only if evidence of lack of antibody response
  - Does not replete IgA, but provides passive specific IgG antibodies
- Rule out meds
  - Cyclosporine, anticonvulsants, captopril, gold, thyroxine, sulfasalazine
Case 5

- 33 year old female presents with fever, chills, productive cough
- Found to have pneumonia
- Further history shows sinusitis 3-4 times a year
- CT for chronic cough shows bronchiectasis
Case 5

- Labs showed CBC with normal WBC, HgB, Plt, but decreased lymphocyte count
- IgG/IgA/IgM checked
  - All lower than detectable limits
- Antibody studies show lack of titers to most vaccines (measles, varicella, tetanus, diphtheria, pneumococcus)
- Low CD 19+ B-cells, normal T cells
CVID

- Common variable immune deficiency
- Primary immune disorder where impaired B cell differentiation leads to impaired antibody production
- Heterogeneous clinical disorders
- Adults and children, 1:25,000-1:50,000
- Recurrent sinupulmonary infections
CVID - Diagnosis

- Low IgG AND low IgA and/or IgM
- Absent antibody response to most or all vaccines (pneumococcus, measles, varicella, tetanus, Hib, diphtheria, etc)
- T & B lymphocytes may be low or normal
- No specific genetic defect has been identified
  - Several gene defects associated, but none diagnostic of disease
CVID - Clinical

• Whole host of comorbidities
  • Autoimmune
    • ITP, AIHA, RA-like, biliary cirrhosis
  • Chronic lung disease (20%)
    • Chronic bronchiectasis
    • Granulomatous lung disease
  • Increased risk of malignancy
    • NHL (8%)
  • Gastrointestinal
    • Malabsorption
CVID - Treatment

- IV – Q4weeks, IV
  - More side effects
  - Nursing required
- SC – Q1week, SC
  - Less side effects
  - More frequent
- SC – Q3-4weeks, SC
  - Hyqvia
  - More volume
  - Single site
Case 6

- 6 year-old boy, long standing eczema
- Further history reveals ITP at age 2
- Has had a few episodes of otitis
- Normal CBC
- Elevated IgA, normal IgG and IgM
Wiskott-Aldrich Syndrome (WAS)

- Rare X-linked disorder, 1:100,000
- Defect in the WASp gene
  - Crucial role in actin cytoskeleton remodeling
  - Impacts site of interaction between T cells and APCs
- Eczema
- Thrombocytopenia
- Sinopulmonary infections (Bacterial and viral)
- Autoimmune – AIHA, neutropenia, vasculitis
WAS - Diagnosis

- Mutation in WASp gene
- High IgA and IgE, normal IgG and IgM
- Decreased T cell number and function
- Lymphocytes devoid of microvillus projections
- Platelet count 20,000-50,000
WAS - Treatment

- Prophylactic Bactrim, Acyclovir for very low T cell counts
- IVIG if evidence of antibody deficiency
- Stem cell transplant can be curative
- Gene therapy promising
18 yo college sophomore is following up with you after hospitalization 2 weeks ago for meningococcal meningitis. HIV antibody was negative. He had an episode of meningococcal meningitis last year after starting school when an outbreak went through his dorm. He received the meningococcal vaccination when he was 15. He is otherwise healthy, and takes no medications. Physical exam today is unremarkable.

Which of the following is most likely to establish a diagnosis?

A: CH50 (total hemolytic complement level)
B: Meningococcal titers
C: Lymphocyte panel
D: IgG, IgM, IgA
24 yo following up with you after an episode of pneumonia 6 weeks ago. She received the pneumococcal vaccine 5 years ago. She tells you that she gets 3-4 sinus infections every year. She also has a chronic productive cough that has never been worked up. Physical exam reveals bibasilar crackles. Review of her hospital chart indicates that HIV antibody is negative.

Which of the following is the most likely diagnosis?

A: Complement deficiency
B: Selective IgA deficiency
C: CVID
D: XLA
30 yo male comes to you after gastroenterologist found absent serum IgA for workup of celiac disease. Patient denies any severe or recurrent infections. IgG, IgM and IgG subclasses are normal. Antibody studies to all vaccines are normal.

What is the next step in treatment?

A: Initiate IVIG therapy
B: Prophylactic antibiotics
C: Revaccinate with pneumococcus and meningococcus
D: Careful observation
Thank You and Good Luck

WE RAN BLOOD TESTS, DID M.R.I. SCANS, TOOK STOOL SAMPLES AND PERFORMED A COLONOSCOPY...AND WE'VE DETERMINED THAT THE “BLOATING SENSATION” YOU’RE EXPERIENCING IS “FAT.”