Foundations of Public Health
Immunology

Primary Immunodeficiency

David Vetter was born in 1971 with X-linked SCID and no functioning immune system. He lived his entire life inside a sterile isolator bubble.

Objectives

• Describe the difference between primary & secondary immunodeficiencies
• Identify signs/symptoms of primary immunodeficiency
• Identify SCID deficiencies, mutations in specific genes
• Describe the difference between X-linked & autosomal recessive inheritance
• Identify specific defects that result in different primary immunodeficiency disorders
• Adaptive & Innate/Other
• Identify treatment options for primary immunodeficiency
• Identify examples of secondary immunodeficiency

Two Types of Immunodeficiency

• Primary (Congenital) Immunodeficiency
  • Diseases caused by genetic defects in the immune system
  • Diseases are not contagious
• Secondary (Acquired) Immunodeficiency
  • Diseases caused by other factors that compromise the immune system
    • Infection (HIV/AIDS), malnutrition, chemotherapy for cancer, removal of spleen, etc.

Primary Immunodeficiency (PI)

• Group of single-gene disorders of the immune system
  • Single-gene defects may lead to a missing enzyme or structural component, developmental arrest at a specific stage of immune development, or nonfunctional proteins
• Nearly 100 separate primary diseases have been described
  • Only ~20 diseases cause the vast majority of PI cases
• Estimates indicate 1 in 500 people in US & Europe have a primary immunodeficiency
  • 80% of people affected are younger than 20 years old
• Diseases often inherited in X-linked recessive fashion
  • 70% of cases occur among males

Primary Immunodeficiency

• Immune disorders vary in severity & spectrum of symptoms
• All primary immunodeficiency cases have increased susceptibility to infections & complications from dysfunctional immune system

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<th>Type of Immunodeficiency</th>
<th>Manifestations and Laboratory Abnormalities</th>
<th>Common Infections/Complications</th>
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<tr>
<td>B cell deficiencies</td>
<td>Abnormal or reduced B cell numbers or function</td>
<td>Reduced antibody levels</td>
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<tr>
<td>T cell deficiencies</td>
<td>Reduced T cell numbers or function</td>
<td>Reduced T cell immunity</td>
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<tr>
<td>Natural killer deficiencies</td>
<td>Reduced NK cell numbers or function</td>
<td>Reduced natural killer activity</td>
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Signs & Symptoms

• Family history of PI
• Classic symptoms include:
  • Increased susceptibility to a variety of infections
  • Ear infections, pneumonia or bronchitis, oral thrush, and diarrhea
  • Multiple infections
  • Children fail to grow and gain weight (failure to thrive)
• Children with untreated SCID rarely live past age to two
Types of Primary Immunodeficiencies:

Adaptive Immune Diseases
- Severe combined immunodeficiency (SCID)
- X-linked SCID
- Autosomal SCID
- DiGeorge Syndrome
- Bare lymphocyte syndrome

- X-lined agammaglobulinemia
- X-linked hyper IgM syndrome
- Common variable immunodeficiency

Severe Combined Immunodeficiency
- Combined B cell and T cell immunodeficiencies constitute 20% of PI diseases
- Most serious forms of primary immunodeficiency
  - Survival beyond first year of life rare without early immune reconstitution through stem cell transplantation (or gene therapy)
  - Early diagnosis critical to improve prognosis for infants who have not had severe opportunistic infections
  - Caused by mutations in 8 different genes

<table>
<thead>
<tr>
<th>Severe combined immunodeficiency (SCID)</th>
<th>Functional deficiencies</th>
<th>Mechanism of defect</th>
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<tr>
<td>X-linked SCID</td>
<td>Development of mature T cells impaired</td>
<td>Loss of mature T cells</td>
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<tr>
<td>Autosomal recessive SCID</td>
<td>Reduced interleukin 2, interferon-γ, reduced serum IgG</td>
<td>X chromosome allele</td>
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<tr>
<td>DiGeorge SCID</td>
<td>Reduced interferon-γ, reduced serum IgG</td>
<td>Autosomal abnormality</td>
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<tr>
<td>Autosomal dominant SCID</td>
<td>Reduced interferon-γ, reduced serum IgG</td>
<td>Autosomal abnormality</td>
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X-linked SCID
- 50% of SCID cases are linked to X chromosome
- From mutation in the interleukin 2 receptor gamma (IL2RG)
- Females may carry the mutation (carrier state), and 50% of her children may get the mutated genes (both male & female, see figure)
- However, only male children will develop the disease
  - Male children have a 50/50 chance of inheriting the gene
  - B cells normal in number, but defective in antibody production

Autosomal SCID
- Combined immunodeficiencies also may result from defective enzymes or other genes
- These diseases are rare, except when consanguinity (incest) or descendants from limited ancestry have children
- Adenosine deaminase (ADA) deficiency
  - Patients have decreased activity of this enzyme
  - Helps cells remove toxic byproducts of metabolism
  - Without the ADA enzymes, these toxins built up in lymphocytes & kills them
- Recombination-activating gene (RAG) deficiency
  - Defective recombinase enzyme
  - Impair V(D)J recombination in B & T cells
  - Unable to create new T & B cell receptors (especially impairs antibody production)

DiGeorge Syndrome
- Rare congenital disease
- Caused by large deletion from chromosome 22
  - DGS gene required for normal development of thymus and related glands
  - Thymus is absent in these patients
  - Difficult to medically counteract loss of this gene
- Symptoms vary greatly between individuals but usually include recurrent infections, heart defects, and characteristic facial features
  - Heart defects and some of speech impairments
  - Loss of T-cells (produced by the thymus) is very difficult to treat

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<th>T cell immunodeficiencies</th>
<th>Functional deficiencies</th>
<th>Mechanism of defect</th>
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<tr>
<td>DiGeorge syndrome</td>
<td>Reduced T cell numbers, normal &amp; decreased serum IgG</td>
<td>X chromosome deletion</td>
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Some of The Known Forms of SCID:

<table>
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<tr>
<th>Gene</th>
<th>Lymphocyte Phenotype</th>
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<tr>
<td>X-linked SCID (gamma chain gene mutations) IL2RG</td>
<td>T(+) B(+) NK(-)</td>
</tr>
</tbody>
</table>

Autosomal SCID
Jak3 gene mutations Jak3 | T(+) B(+) NK(-) |
ADA gene mutations ADA | T(+) B(+) NK(-) |
IL-7R alpha-chain mutations IL7R alpha | T(+) B(+) NK(-) |
CD3 delta or epsilon mutations CD3 delta or epsilon | T(+) B(+) NK(-) |
RAG1/RAG2 mutations RAG1/RAG2 | T(+) B(+) NK(-) |
Artemis gene mutations ARTEMIS | T(+) B(+) NK(-) |
CD45 gene mutations CD45 | T(+) B(+) NK(+) |

DiGeorge Syndrome
- Deletion of genes in DiGeorge syndrome can be visualized by a fluorescent signal on only one of the two couples of chromosome 22.
**X-linked agammaglobulinemia (XLA)**
- Failure of B cell precursors to mature into B lymphocytes and ultimately plasma cells
  - Mutations in BTK gene located on X chromosome
- Need plasma cells to produce gamma globulins
- Results in severe deficiencies of all serum Ig isotypes, as well as reduced numbers of B cells
- 25% of patients also develop autoimmune diseases, commonly arthritis

**X-linked Hyper IgM Syndrome (XHIM)**
- Inherited disorder of the immune system that affects immunoglobulins & impacts only males
  - Also can be autosomal recessive (much rarer) that can affect both males & females
  - Caused by a mutation in the CD40 ligand gene
  - CD40L expressed on activated CD4+ T cells
  - Characterized by susceptibility to infections and low levels of serum immunoglobulins
    - IgG, IgA and IgE are low
    - IgM may be low, normal or elevated

**Bare lymphocyte syndrome**
- No production of MHC I or MHC II molecules
  - Most common type is failure to synthesize MHC I
- Compromises antigen presentation
- Few functional CD4+ T cells
- Inherited autosomal recessive genes

**Common Variable Immunodeficiency**
- Group of disorders that form most common primary immunodeficiency
- Exact cause is unknown, and clinical symptoms vary by patient
- Characterized by low levels of serum immunoglobins, increased susceptibility to infections
  - Most patients have normal numbers of B cells, but fail to undergo normal maturation into plasma cells
  - Results in poor antibody responses and reduced serum levels of IgG, IgA, and IgM
  - Some patients have defects in helper T cell function
  - Another group of patients have excessive numbers of cytotoxic T cells
  - Complication include lung damage, enlarged lymph nodes & spleen, arthritis and cancer
**Types of Primary Immunodeficiency: Innate Immune & Other Disorders**

- Chronic granulomatous disease
- Leukocyte adhesion deficiency
- Complement deficiencies
- Chediak – Higashi syndrome
- Wiskott - Aldrich syndrome
- Ataxia - telangiectasia

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**Chronic Granulomatous Disorder (CGD)**

- Rare, inherited disorders caused by defects in phagocytes
- Phagocytic cells cannot kill certain microorganisms
- Phagocytes move normally and ingest microorganisms, but unable to kill specific types of bacteria and fungi
- Cannot process oxygen properly to create oxygen-containing compounds needed for killing
- Children usually healthy at birth, but soon develop recurrent bacterial or unusual fungal infections
- CGD patients vulnerable to severe recurrent bacterial and fungal infections
- Chronic inflammatory conditions including gingivitis, enlarged lymph glands, or granulomas are common

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**Chediak Higashi Syndrome (CHS)**

- Rare childhood autosomal recessive disorder that affects multiple systems of body
- Hypopigmentation of skin, eyes, and hair
- Prolonged bleeding, bruise easily, and recurrent infections
- Mutation in CHS gene affects synthesis of storage/secretory granules in various types of cells
- Abnormal natural killer cell function
- Defective lysosomal function in macs, dendritic cells and neutrophils
- Often fatal in childhood as a result of infection or an accelerated lymphomalike phase
- Few patients live to adulthood

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**Leukocyte Adhesion Deficiency (LAD)**

- Very rare disease with fewer than 200 patients reported
- Characterized by leukocytosis and localized bacterial infection
- Difficult to detect until infections have progressed to life-threatening level
- Disorder results when patient cannot produce CD18 protein
  - CD18 is necessary for leukocytes to travel to the site of an infection
- Leukocyte adhesion deficiency type I (LAD I)
  - Failure to express the CD18 integrin, a receptor for C3b on myeloid, lymphoid cells
  - No CD18 on lymphocytes, monocytes, and neutrophils
  - Patients succumb to infection (mostly bacterial), commonly when younger than 2 years
- Leukocyte adhesion deficiency type II (LAD II)
  - More rare than type I
  - Defect in expression of ligand for T and F soldiers (remember those?)
  - Patients have leukocytosis, recurrent infections, severe growth and mental retardation
  - Usually do not die from infection, but also may have neurologic impairment, and short stature

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**Wiskott-Aldrich Syndrome (WAS)**

- X-linked recessive genetic condition, found almost exclusively in males
- Disorder causes persistent thrombocytopenia, IgM deficiency
- Reduced number of platelets, eczema, combined immunodeficiency, and higher risk of developing autoimmune diseases
- Results from defect in protein called Wiskott-Aldrich syndrome protein (WASP)
- WAS protein important for migration and mortality of immune cells
  - Platelets and leukocytes are smaller, do not develop properly, & fail to migrate

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**Ataxia telangiectasia (AT)**

- Autosomal recessive disorder is a multi-system disease
- Characterized by gait abnormalities (ataxia) & vascular malformations (telangiectasia)
- Affects brain, skin & immune system
- Mutation in AT gene impairs DNA repair during recombination of antigen receptor genes
- Compromises T cell maturation & function
- AT patients may have defective isotype switching, from dysregulation of immunoglobulin gene superfamily
- AT protein also controls cell cycle & mutation of this gene on chromosome 11 may explain immunologic & neurologic symptoms
Complement Deficiencies

- Patients with antibody or complement deficiencies can have near-normal life spans
- Complement deficiencies are rare (less than 2% of immunodeficiencies)
- We will concentrate on C2, C4, and C3 deficiencies

C2 & C4 Deficiencies

- Associated with recurrent infections by encapsulated bacteria (antibodies, complement and neutrophils required for proper clearance)
- C2 is most widely reported deficiency of all the components in the complement pathways
- Immune complex disorders are main problem with C2 deficiency
  - Skin and joint manifestations are common
  - Frequently found in patients with SLE, Henoch-Schonlein vasculitis, polymyalgia, and recurrent pyogenic infections
  - Most individuals with C2 deficiency are asymptomatic (until disease development)
- Almost all patients with complete C4 deficiency have discoid or systemic lupus erythematosus (with or without associated glomerulonephritis)
- Need classical pathway to eliminate immune complexes
- Classical pathway is impaired in C2 & C4 deficiency
  - Not susceptible to infection (like C3 deficiencies) because alternative pathway still available to protect host defenses

C3 Deficiencies

- C3 deficiency may be due to a primary defect in the C3 gene or expression of the C3 protein
- Deficiencies predispose person to frequent bouts of pyogenic bacterial infections (especially Gram-negative bacteria such as meningococci and pneumococci) and immune complex disease
  - Approximately, 78% of patients with C3 deficiency have repeated infections and 79% of patients experience autoimmune disorders (such as arthralgia and vasculitic rashes, lupuslike syndrome, and membranoproliferative glomerulonephritis)

Primary Immunodeficiency Treatment

- Need effective and early treatment
  - Untreated primary deficiencies characterized by frequent life-threatening infection, debilitating illnesses
  - Usually fatal if untreated
  - Medical advances in treatment allow patients to survive childhood & live almost normal lives
  - Requires life long therapy including IV gamma globulin infusions, antibiotic therapy, or bone marrow transplantation

Treatment Options

- Bone Marrow transplantation
  - Undifferentiated stem cells taken from healthy bone marrow are injected into SCID patients
  - Stem cells can then differentiate into healthy immune cells
- Antibiotics
  - Patients often treated with IV antibiotics for bacterial infections
  - Also as a prophylactic method to prevent recurrent infections
- Antibody replacement therapy
  - Intravenous (IV) infusion of plasma with protective IgG antibodies in large doses
  - Helps reduce severity and frequency of infections
Treatment Options: Gene Therapy

- New technology that attempts to replace or repair abnormal genes in patients
  - Repair abnormal cells by introducing normal gene & then return “new” normal cells to person
  - Or target cells inside body & fix bad genes inside cell with viral vectors
- Proven successful in two forms of SCID
  - ADA SCID & X-linked SCID
- But, serious adverse effects reported in association with gene therapy, not available in US
- Virus vectors caused disease, by turning on oncogenes to cause cancer

Secondary Immunodeficiency

- Acquired immunodeficiency
- More common than primary deficiencies
- Causes include non-immune disorders (diabetes, malnutrition) and immunosuppressive treatment
- Prolonged serious illness may also lead to impaired immune response
- Impairment is often reversible

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<thead>
<tr>
<th>Cause</th>
<th>Mechanism</th>
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<tr>
<td>HIV-associated immunodeficiency virus infection</td>
<td>Depletion of CD4+ helper T cells</td>
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<tr>
<td>Protein caloric malnutrition</td>
<td>Metabolic aberrations interfere lymphocyte maturation and function</td>
</tr>
<tr>
<td>Infections and chemotherapy treatments for cancer</td>
<td>Decreased bone marrow precursors for all leukocytes</td>
</tr>
<tr>
<td>Cancer metastases to bone marrow</td>
<td>Reduced site of leukocyte development</td>
</tr>
<tr>
<td>Removal of spleen</td>
<td>Decreased neutrophilia</td>
</tr>
<tr>
<td>Removal of thymus</td>
<td>Decreased thymic function</td>
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In Summary

- Understand the difference between primary & secondary immunodeficiencies
- Identify SCID deficiencies, mutations in specific genes
- Understand the difference between X linked & autosomal recessive inheritance
- Identify specific defects that result in different primary immunodeficiency disorders
- Adaptive & Innate/Other
- Identify treatment options for primary immunodeficiency
- Identify examples of immunodeficiency

Self-Test Questions

- Describe the difference between a primary & secondary immunodeficiency. Name 3 examples of each type.
- Describe how the patterns of inheritance (X linked & autosomal recessive) are different.
- What is SCID? How does this impact the immune response? What genetic defect causes X linked SCID?
- What is consanguinity? Which PI diseases are linked to this?
- What defect causes DiGeorge’s Syndrome? CGD? Chediak Higashi Syndrome? WAS? AT? Describe the phenotype (problems) that occurs in each of these patients.
- Identify and describe the 4 different treatment options available for primary immunodeficiency.