Overview

- Four major categories of primary immunodeficiency (PID)
- Clinical conditions associated with PID
- Types of infections and organisms associated with each category of PID
- Laboratory testing algorithms for diagnosis
- Treatment

Case #1

- 3-month month-old Hispanic girl with 2-week history of lymph node swelling in neck and skin abscesses
- A cousin died at a young age after undergoing bone marrow biopsy in Mexico (diagnosis – unknown)
- CBC – WBC 21K, normal differential, H/H and platelet count
- Lymph node biopsy
  - Necrotizing granulomatous lymphadenitis
  - Culture - Candida lusitaniae
- Recurrent skin abscesses – Staphylococcus aureus, Serratia marcescens

Case #2

- A 2-year year-old boy was diagnosed with Streptococcus pneumoniae meningitis.
- One year earlier, he was treated for Haemophilus influenzae type b meningitis
- No evidence of skull fracture or CSF leak from nose or ear
- CH50 – 0
- Complement 2 (C2) - low

Case #3

- 13-year year-old girl developed viral meningoencephalitis twice within a year and has history of recurrent herpes simplex infections.
- In addition, she started having recurrent ear and sinus infections.
- History of hypothyroidism and vitiligo
- Low serum IgG, IgM and IgA levels, with low titers to pneumococcal vaccine and Candida antigens

Primary Immunodeficiency (PID)

- Results from inherited genetic defects that involve immune system and responses
- As many as 1 in 2000 live births
- Primary Immunodeficiencies may become apparent
  - Soon after birth
  - After loss of maternal antibodies
  - Milder forms - second or third decade
- Some of rarer – Complement deficiencies
- Others, like DiGeorge syndrome, diagnosed more commonly
- Selective IgA deficiency may occur in as many as one in every 300 persons.
Prevalence of PID

- > 150 distinct defects resulting in PIDs to date
  - Causative gene known in 80%
- Classified according to the primary immunological mechanism that is altered
  - Antibody / B-cell deficiencies
  - Cellular (T-cell) and combined T- and B-cell disorders
  - Innate/Phagocytic deficiencies
  - Complement disorders

Humoral
49%

Phagocytic
19%

Cellular
15%

Complement
2%

Combined
25%

Clinical Conditions Associated with PID

- Infections...
  - Recurrent
  - Unusually severe
  - Unusual or opportunistic organisms
  - Failure to clear infections with oral antibiotics
- Types of infections
  - Sinupulmonary infections
  - Gastrintestinal resulting in chronic diarrhea
  - Oral thrush
  - Abscesses
  - Skin lesions
- Malabsorption
- Failure to thrive
- Incomplete healing of wounds
- Physical anomalies
- Adverse reactions to live vaccines
-Absent thymic shadow on x-ray

B-Cell / Humoral Disorders

- Mode
  - Lack of antibody (production/response)
  - IgA deficiency – lack of IgA to opsonize organisms on mucosal epithelium (bowel diseases)
  - No antibody to bind C’
- Types of infections
  - Mucosal surfaces
  - Sinupulmonary (pyogenic bacteria)
  - Gastrintestinal (Giarda, enterviruses)
- Associated infectious agents
  - Staphylococcus aureus
  - Streptococcus pneumonia
  - Hemophilus influenzae, type b
  - Neisseria meningitidis
  - Giardia lamblia
  - Cryptosporidium species
  - Enteroviruses

T-Cell or Combined T-Cell/ B-cell PID

- Mode of Immunodeficiency
  - Lack of T-cell antigen recognition/help
  - More often T-cell deficiencies associated with combined PID due to T-cell role in development of antibody response
- Types of infections
  - Pneumonias
  - Opportunistic infections
- Associated infectious agents; almost all of them...
  - Candida albicans
  - Pneumocytsis spp
  - Mycobacterium species
  - CMV
  - EBV
  - enteroviruses

B-cell Deficiencies

<table>
<thead>
<tr>
<th>B-cell Defect</th>
<th>Associated clinical/laboratory findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruton’s agammaglobulinemia or X-linked \ agammaglobulinemia (XLA): defect in Bruton’s Tyrosine Kinase (BTK)</td>
<td>Serious infections caused by common pyogenic encapsulated bacteria, no vaccine-specific Abs, and/or development of vaccine-related illness</td>
</tr>
<tr>
<td>Common variable \ immunodeficiency (CVID): Deletion of a segment of chromosome 22</td>
<td>Low antibody production in general and in response to vaccines</td>
</tr>
<tr>
<td>Chronic mucocutaneous candidiasis</td>
<td>Recurrent oral, esophageal or skin infection caused by Candida species</td>
</tr>
</tbody>
</table>

T-Cell and Combined Deficiencies

<table>
<thead>
<tr>
<th>T cell Defect</th>
<th>Associated clinical/laboratory findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCID</td>
<td>Failure to thrive, chronic diarrhea, oral thrush, recurrent or severe bacterial, viral and/or fungal infections</td>
</tr>
<tr>
<td>CD40 and CD40 ligand deficiency</td>
<td>Recurrent sinupulmonary and opportunistic infections with low IgG and IgA levels, variable IgM</td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>Easy bruisingability, eczema, recurrent otitis media, diarrhea, thrombocytopenia with sm. platelets</td>
</tr>
<tr>
<td>DiGeorge syndrome</td>
<td>Hypoparathyroidism, cardiac malformations, dysmorphic features, variable T- and B-cell defects</td>
</tr>
<tr>
<td>X-linked lymphoproliferative disease (XLP)</td>
<td>Hypergammaglobulinemia, persistent or fatal EBV infection</td>
</tr>
<tr>
<td>Chronic mucocutaneous candidiasis</td>
<td>Recurrent oral, esophageal or skin infection caused by Candida species</td>
</tr>
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</table>
**Phagocytic Deficiencies**

- **Mode of immunodeficiency**
  - Qualitative – dysfunctional phagocytes
  - Chemotaxis, adhesion, and killing
  - Quantitative – neutropenia
- **Types of infections**
  - Skin
  - Reticuloendothelial system
  - Abscesses
- **Associated infectious agents**
  - Pseudomonas species
  - Klebsiella species
  - Staphylococcus aureus
  - Candida albicans
  - Nocardia species
  - Aspergillus species

**Complement Deficiencies**

- **Mode of Immunodeficiency**
  - Defects in all C' proteins have been described
  - Since most C' genes are autosomal, heterozygous defects often do not result in increased risk of infections.
  - Symptomatic individuals are usually homozygous for a defect
  - Many C' deficiencies associated with autoimmune inflammatory pathology – glomerulonephritis, vasculitis, SLE, chronic recurrent angiokeratoma
- **Types of infections**
  - Septicemia
  - Septic arthritis
  - Meningitis
- **Associated infectious agents**
  - Defects in classical pathway
    - Pyogenic bacteria
  - Defects in later components (C5–C8)
    - Neisseria meningitidis
    - Neisseria gonorrhoeae
  - Defects in mannose binding lectin pathway
    - Streptococcus pneumoniae
    - Neisseria meningitidis

**Phagocytic Cell Deficiencies**

<table>
<thead>
<tr>
<th>Example</th>
<th>Innate immunologic component involved</th>
<th>Clinical manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chediak-Higashi syndrome</td>
<td>Defects of granule formation and content</td>
<td>Partial albinism, giant lysosomes, low NK and CTL, recurrent bacteria infections</td>
</tr>
<tr>
<td>Chronic granulomatous disease (CGD)</td>
<td>Defect in oxidative metabolism (NADPH oxidase)</td>
<td>Widespread granuloma formation, increased susceptibility to bacterial and fungal infections</td>
</tr>
<tr>
<td>Leukocyte adhesion deficiency Type 1 (LAD1)</td>
<td>Defective adherence and chemotaxis as a result of CD15 and CD18 defects</td>
<td>Delayed cord separation, skin ulcers, periodontitis, leukopenia</td>
</tr>
<tr>
<td>BCGosis</td>
<td>Defects in INF-γ and IL-12</td>
<td>Susceptibility to Salmonella and mycobacteria</td>
</tr>
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**Clues to Lead to Suspicion of PID**

- **Extensive history and physical exam**
- **Family history of inherited disorders**
- **Child’s development**
- **Immunization records**
- **Red flags**
  - > 8 infections in the past year
  - No weight gain, failure to thrive
  - Opportunistic infections
  - Oral antibiotics ineffective
  - Positive family history
  - Live vaccine complications
- **Physical anomalies**
- **Laboratory values**
- **Autoimmunity**
- **Rule out secondary and/or acquired immunodeficiencies (HIV, chemotherapy for malignancy or autoimmune disorders)**

**Age at Presentation May Provide Clues**

<table>
<thead>
<tr>
<th>Age at Presentation</th>
<th>Associated PIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal period</td>
<td>Omenn syndrome, Severe congenital neutropenia, DiGeorge syndrome, Leukocyte adhesion disorder</td>
</tr>
<tr>
<td>&lt;6 – 12 months</td>
<td>SCID, Other T cell immunodeficiency, CD40 ligand deficiency</td>
</tr>
<tr>
<td>6 months – 5 years</td>
<td>Wiskott-Aldrich syndrome, DiGeorge Syndrome, Chronic mucocutaneous candidiasis, Hypogammaglobulinemia, Phagocytic defect - CGD</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>Late presentation of above, Ataxia telangiectasia, Common variable immunodeficiency, Specific antibody defect, Complement disorder</td>
</tr>
</tbody>
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**Initial Laboratory Workup for Suspected PID**

- **Complete blood count and differential with absolute counts**
- **Lymphocytes subset enumeration by flow cytometry**
- **Quantitative immunoglobulins (IgG,IgM,IgA)**
  - Age specific normals
- **Complement profile**
  - Total hemolytic complement - CH50
  - AH50
- **Delayed Type Hypersensitivity (DTH) panel**
  - Skin test reactivity limited until 1 year of age
  - 75% of children 12–36 months of age respond to Candida antigens
**Phagocytic disorders**

- Antimicrobial prophylaxis
- Titers to specific vaccines (DT, pneumococcal)
- Oxidative burst assay (NBT/DHR)
- SCID
- Possible innate

**Phagocytic deficiencies**

- Kostman
- Bone marrow transplant
- Phagocytic disorders

- (Anti-B IV immunoglobulins (IVIG) or subcutaneous
- stain
- X
- X
- For which preventative therapy is available
- Hyper IgE

- 4 categories based immune defect
  - Bone marrow transplant
  - Phagocytic deficiencies
  - IV immunoglobulins (IVIG) or subcutaneous
  - Enteroviruses
  - Myeloperoxidase
  - Syndrome
  - Phagocytosis
  - Possible
- **Treatment**

- Common variable ID (CVID) or other B-cell ID

- Suspected T-cell / Combined T- and B-cell ID

- Pneumonia, sinopulmonary infections, severe viral, fungal infections

- Lymphocyte stimulation assays (LSA) - antigen specific and non-specific

- Low T-cells
- Low LSA
- Possible SCID
- Further testing

- Low T-cells
- Low LSA
- Hypogammaglobulinemia
- Abnormal facial features

- Low-antigen specific LSA (CanSibs)
- Mitogen induced cytokine assays
- Possible chronic mucocutaneous candidiasis

- Suspected Complement Deficiency

- Sepsis (pyogenic bacteria, Neisseria spp)
- Glomerulonephritis
- Autoimmune disease

- Total Hemolytic C' (CH50)
- Anti-C' component

- Low IgG or C'P
- Hypogammaglobulinemia

- Low Complement
- Individual Complement testing
- Complement deficiency

- Sinopulmonary and Gastrointestinal Infections

- • Enteric bacteria
- • Pyogenic and mycobacteria
- • Neisseria

- Low IgG or C'P
- B-cell ID
- Low C'P
- Possible hyper-IgE syndrome

- Suspected Complement Deficiency

- Sepsis (pyogenic bacteria, Neisseria spp)
- Glomerulonephritis
- Autoimmune disease

- Total Hemolytic C' (CH50)
- Anti-C' component

- Low IgG or C'P
- Hypogammaglobulinemia

- Low Complement
- Individual Complement testing
- Complement deficiency

- Suspected B cell Deficiency

- Sinopulmonary and Gastrointestinal Infections

- • Enteric bacteria
- • Pyogenic and mycobacteria
- • Neisseria

- Low IgG or C'P
- B-cell ID
- Low C'P
- Possible hyper-IgE syndrome

- Suspected Phagocytic Deficiency

- Skin, reticuloendothelial system, abscesses
- (Staphylococcus, enteric bacteria, fungi, mycobacteria)

- • Neutrophil oxidative burst assay (NBT/DHR)
- • Neutrophil receptor assay (CD11b/CD18)
- • Myeloperoxidase stain
- • IgE

- Suspected Complement Deficiency

- Sepsis (pyogenic bacteria, Neisseria spp)
- Glomerulonephritis
- Autoimmune disease

- Total Hemolytic C' (CH50)
- Anti-C' component

- Low IgG or C'P
- Hypogammaglobulinemia

- Low Complement
- Individual Complement testing
- Complement deficiency

- Suspected T-cell / Combined T- and B-cell ID

- Pneumonia, sinopulmonary infections, severe viral, fungal infections

- Lymphocyte stimulation assays (LSA) - antigen specific and non-specific
Summary

- PID can result as a defect in any arm of immune system: humoral, cellular/combined, phagocytic, complement.
- Recurrent severe infections are hallmark of PID
- Types of infections and types of organisms can provide clues to which arm of immune system affected to help in deciding which laboratory tests are appropriate for diagnosis
- Common laboratory testing can often give significant clues presence and possibly type of immunodeficiency.

References

- ARUP Consult:  www.arupconsult.com