Recognition of Primary Immune Deficiency
in infants younger than 6 months

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DEPARTMENT OF PEDIATRICS

Learning objectives:
- Explain the TREC newborn screening test for severe combined immunodeficiency
- Discuss conditions presenting in the first six months of life
- Recognize when a referral is necessary
- Appreciate that severe combined immunodeficiency is a medical emergency
Symptoms, infection, treatment, response
Patient returns to health
(repeat)

Symptoms, infection, treatment, response
Symptoms, infection, treatment, response
Symptoms, infection, treatment, response
Symptoms, infection, treatment, persistence

Preliminary Diagnosis: somethin’ ain’t right

Could this be...

- Recurrent infections
- Protracted infection
- Unexpected complications of infection
- Chronic diarrhea
- Interstitial pneumonia
- Therapy-resistant mucocutaneous candidiasis

severe immunodeficiency?

Immunology Refresher Course
Organ that play a large role

<table>
<thead>
<tr>
<th>Thymus</th>
<th>Liver</th>
<th>Tonsils</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodes</td>
<td>Spleen</td>
<td>Blood</td>
</tr>
</tbody>
</table>

Organs that play a large role

Major components & functions

**Adaptive Immunity**
- B lymphocytes
- Antibodies
- Effector T cells

**Innate Immunity**
- Epithelial barriers
- Phagocytes
- Complement
- Natural killer cells

Surveillance

Unlike most body systems, major cell types of the immune system leave their organs and roam around the body looking for trouble.

The cells, cell products and supporting organs cooperate to effect protection.

Bajenoff M. Immunity 2006;25:989
Innate immunity

Includes invariant receptors with fixed pattern recognition.
> one signal
> no memory

Adaptive immunity

Mutable receptors with evolving pattern recognition.
> two signals
> durable memory

Immune tolerance

Don’t respond if it isn’t a threat

Primary Immunodeficiency
General Concepts

NORMAL: Element (cell or molecule) is present in normal amounts and working properly;
Example – Protective cytotoxic T-cell responses

DEFECTIVE: Element (cell or molecule) is present in normal amounts, NOT working properly;
Example – Calcium channel defect in T-cells.

DEFICIENT: Element (cell or molecule) is at low levels or missing entirely;
Example – Adenosine deaminase deficiency

PIDDs General Classification
Genetically determined; inherited or new mutation

<table>
<thead>
<tr>
<th>PID Category</th>
<th>Defect</th>
<th>Components</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined Immune Deficiency</td>
<td>Inability to generate any adaptive responses</td>
<td>T, B, NK cells</td>
<td>Toxic metabolite, Differentiation, Receptor expression, DNA repair, Cytokine signaling</td>
</tr>
<tr>
<td>T cell defects</td>
<td>Inability to mount adaptive killer cell responses</td>
<td>T cells</td>
<td>Thymic apoptosis, Signal transduction, TCR signaling, Cytokine signaling</td>
</tr>
<tr>
<td>Autoimmune Thrombocytopenia</td>
<td>Inability to mount adaptive antibody responses</td>
<td>B cells</td>
<td>Lineage commitment, Antibody expression, BCR signaling</td>
</tr>
<tr>
<td>Neutrophil defects</td>
<td>Inability to ingest / kill bacteria</td>
<td>PMN</td>
<td>Dysregulation, Multiple signaling</td>
</tr>
<tr>
<td>Dying mutation</td>
<td>Multiple</td>
<td>Multiple</td>
<td>Various</td>
</tr>
</tbody>
</table>

PIDD – Primary Immune Deficiency Disorder

Inheritance

• X-linked
  – Male disease, female carrier state
  – 20% of SCID is X-linked

• Autosomal recessive
  – Disease present if mutation on both alleles
    • Homozygous: same mutation both alleles
    • Compound heterozygous: different mutation on each allele
  – Carrier state if mutation in one allele

• Autosomal dominant
  – Disease present, mutation on one allele
In the timeframe birth – 6 months

T-cell defects predominate

Combined defects present early
The defect is not intrinsically fatal – death is secondary to infection

Overall incidence is low

- Life-threatening defects ~ 1/100,000 births
- 50 new cases of SCID per year in the US
- May vary by state
  - California 1/33,000, Wisconsin ~1/100,000
- May vary by community
  - California hispanic population 1/22,000
  - Navajo, Apache 1/2,500
- Early diagnosis is critical

SCID – Severe Combined Immune Deficiency

When should you consider PIDD?
Certain findings on physical exam

- Anhydrotic ectodermal dysplasia – absence of nails, hair; no sweating (NEMO)
- Pigmentary dilution (Griscelli, Hermansky-Pudlak, Chediak-Higashi)
- Truncal short stature (spondyloepiphyseal dysplasia), hypoplastic iliac wings, hyperpigmented macules (Schimke Immuno-Osseous Dysplasia)
- Short limb dwarfism, incomplete extension at elbow, flaring of ribs at costochondral junction (Cartilage Hair Hypoplasia)

"Missing" organs

- No detectable thymus
- No detectable tonsils
- No detectable lymph nodes

Bone marrow failure

Pancytopenia

Abnormal facies

- DiGeorge Syndrome: "pixie-like face" with bulbous nose tip, small mandible, malar flatness, short ears with folding of pinna, "hooded" eyelids.
- Down Syndrome: Macroglossia, upward slanting palpebral fissures
- Nijmegen Breakage Syndrome: "bird-like face" with receding forehead and mandible, long nose, long philtrum, large ears.
- CHARGE Syndrome: Coloboma, heart defects, choanal atresia, retardation of growth, genital hypoplasia, ear abnormalities/deafness.
Unusual rashes

Eczema not distributed like atopic dermatitis; not an “itch that rashes”

> defective DC chemotaxis

(Wiskott-Aldrich S.)

Scaling, erythematous maculopapular eruption spread widely over the trunk and extremities, with near-erythroderma in some patients

> graft vs. host caused by maternal T-cells

(SCID) or (Omenn's syndrome)

Less specific findings that suggest PIDD

- Microcephaly
- Hypocalcemic tetany, truncoconal heart defect
- Anemia, Thrombocytopenia
- Alopecia, hypereosinophilia, elevated IgE, lymphadenopathy, hepatomegaly, erythroderma
- Unexplained failure to thrive (weight)

Think about PIDD when infections are

- Persistent
- Thrush
- Recurrent
  - Pneumonia, otitis, skin abscesses
  - Chronic or indolent
  - Cough, dyspnea, respiratory tract obstruction
  - Unresponsive to standard treatments
  - Pneumonia, sepsis, diarrhea
  - Unusually severe or prolonged
    - Varicella x 3 weeks
  - Caused by unusual or opportunistic organism
    - Mycobacterium avium, Pneumocystis jiroveci
  - Rare
    - Herpes Simplex meningoencephalitis
Unusual abscesses, skin infections, candidiasis

Omphalitis with failure of the cord to separate (Neutrophil defect such as Kostmann S., LAD 1, J.)

Persistent candidiasis that fails to resolve with repeated treatment (CD4 T-cell defect such as SCID, Dectin, CARD9, APECED, IL17 def.)

How do you make a diagnosis?

A.S.A.P.

- SCID is uniformly fatal by age 2 yrs without immune reconstitution
- Some standard procedures can be fatal
  - rotavirus vaccine
  - blood transfusion
- Treatments are available
  - stem cell transplant, thymus transplant, enzyme replacement, gene therapy
- Favorable response to treatment depends on early diagnosis
A.S.A.P.

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T-Cell Receptor Excision Circles (TRECS)

~ 70% are 8Rec-psiα

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Data for 20 SCID cases, California

In the timeframe birth – 6 months

Finding a needle in a haystack
Pilot Programs outside Texas

<table>
<thead>
<tr>
<th>State</th>
<th>Screened Flow Cytometry</th>
<th>Abnormal</th>
<th>PIDD</th>
<th>SCID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass</td>
<td>77,000</td>
<td>51</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>100,597</td>
<td>78</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Wisc</td>
<td>71,000</td>
<td>11</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>~100,000</td>
<td></td>
<td></td>
<td>GeneDx unk</td>
</tr>
<tr>
<td>Calif</td>
<td>265,554</td>
<td></td>
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</table>

California instituted full screening Aug 1, 2010 – SCID overall 1/33,000

Texas SCID Pilot Study

- Collaborating with New England Newborn Screening Program, funding from CDC
  - Complements data from MA, WI pilots
- One TX hospital (St. David’s Medical Center, Austin)
- Positive results shared with primary care provider and a pediatric immunologist
  - Recommendation for a referral to a local immunologist to obtain a diagnostic test and evaluation
- Establish optimal methodology for use when funding is available.

Screening by Primary Care Physician

- TRECS
  - State Newborn Screening lab
    - Detects most T-cell defects
  - CBC with differential
    - Absolute lymphocyte counts
    - Absolute neutrophil counts
    - Platelet counts
- Immunoglobulins
  - IgG, IgA, IgM, IgE

CCMC Clin-Path lab

Not yet available
Screening by Subspecialist

Initial flow cytometry
Cincinnati Diagnostic Immunology Lab
CD3+ T-cells
CD3+ CD4+ T-cells
CD3+ CD8+T-cells
CD3+ CD4+ CD45RO+ memory CD4 T-cells
CD3+ CD8+ CD45RO+ memory CD8 T-cells
CD3+ CD56+ natural killer cells
CD19+ B-cells

1-2 mL of whole blood collected in sodium heparin tubes

Confirmatory testing

• Targeted flow cytometry
• Targeted protein assays
• Functional assays
  – Reference labs
  – Commercial labs
  – Research labs at referral centers
    • UT SW Dallas
    • Baylor Texas Children’s Hospital Houston

Genetic sequencing
Seattle Diagnostic Immunology Lab
What if diagnosis is delayed?

Impact of delayed diagnosis

Chan A. Clin Immunol 2011;138:3-8
Early testing enhances chance of survival (right chart is families with a history of SCID who elected testing at birth)

Early transplant enhances survival (patients with no family history, diagnosed and treated)

Current recommendation is transplant before 3.5 months

Chan A. Clin Immunol 2011; 138: 3-8

Buckley R. J Pediatr. 2009; 155: 834
**HSC Donor selection**

- 128 treated
  - 88% survived HLA matched sibling donor
  - 68% survived HLA matched parent T-cell depleted
  - 87% survived Mismatched, unstimulated adult or cord blood

*Chan A. Clin Immunol 2011; 138: 3-8*

**Confirmed by UK experience**

<table>
<thead>
<tr>
<th>Family Hx (60)</th>
<th>No Family Hx (48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at Ds</td>
<td>144 (1-455)</td>
</tr>
<tr>
<td>Infections</td>
<td>89%, mostly multiple</td>
</tr>
<tr>
<td>Pathogens</td>
<td>PCP, candida, 63 other</td>
</tr>
<tr>
<td>Death before transplant</td>
<td>17/48 (35%)</td>
</tr>
<tr>
<td>Survival with any transplant</td>
<td>13/24 (54%)*</td>
</tr>
<tr>
<td>Survival with haploidentical transplant</td>
<td>8/16 (50%)</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>90%</td>
</tr>
</tbody>
</table>

*Subset of transplant within 10 yrs of each other

*Brown L. Blood 2011; (prepublication)*

**If SCID is suspected**

- Immediately stop breast feeding unless mother is CMV(-)
- Positive pressure isolation to avoid infection
- Do not vaccinate
  - patient cannot respond
  - live attenuated viral vaccines will cause infection
  - if live attenuated vaccine has been given (e.g., BCG), consider treating
- Transfusions (only if needed)
  - CMV negative only
  - Irradiated blood products only (to avoid GVHD)
• Evaluate for RSV, PCP
• Begin prophylaxis for Pneumocystis, mycobacteria, fungal infections
• TPN if patient has FTT or intractible diarrhea
• Begin immunoglobulin replacement therapy
  – Trough > 800 mg/dL

TPN – total parenteral nutrition

Long-term outcomes

• GVHD remains a problem in some cases
• B(+) SCID do better than B (–)
• Radiosensitive SCID have cognitive, growth & development issues
• Unconditioned transplants can result in autoimmunity
• ~60% require lifelong IgG replacement therapy
• Early organ damage (lungs) persists

Resources

• Web
  – http://www.immunodeficiencysearch.com
  – http://www.primaryimmune.org/

• Consultations
  – Local experts, Dallas, Houston, or

bert.slaide@healthpoint.com