SCID

- The Disease
- Diagnosis
- Treatment
- Outcomes: Early vs. Late Treatment

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Goals

• Introduction to SCID
• How SCID is diagnosed
• Newborn Screening for SCID
• How SCID is treated
• Overview of outcome data regarding early vs. late treatment
SCID - The Disease

- 1976 Made-for-TV movie
- David Vetter born 1971
Relative Incidence of PID

- Antibody Deficiency (53%)
- Complement Deficiency (1%)
- PMN Dysfunction (14%)
- Combined Immunodeficiency (23%)
- Cellular Immunodeficiency (7%)
- Other (2%)

Skoda-Smith and Barrett, Contemporary Pediatrics 17:156-165
Components of the Immune System

- Complement
- Antibodies
- T Cell
- B Cell
- Neutrophil
- Macrophage

Centrifuge

Red Blood Cells

Plasma
The Immune System

**Complement**

“Land Mines”

**Phagocytes**

“Marines”

- Neutrophils
- Macrophages

Host Defense
• Now ~21 different Genetic defects associated with SCID
• 1st ADA Deficiency (1972)
**Naïve T cells are Reduced in All Forms of SCID**

**Common Feature**  **ABSENT/NON-FUNCTIONAL T CELLS**

<table>
<thead>
<tr>
<th>Condition</th>
<th>T-</th>
<th>B+</th>
<th>NK-</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL2Rγ</td>
<td>T-</td>
<td>B+</td>
<td>NK-</td>
</tr>
<tr>
<td>JAK3</td>
<td>T-</td>
<td>B+</td>
<td>NK-</td>
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<td>T-</td>
<td>B+</td>
<td>NK+</td>
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<tr>
<td>CD45</td>
<td>T-</td>
<td>B+</td>
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<tr>
<td>RAG1</td>
<td>T-</td>
<td>B-</td>
<td>NK+</td>
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<tr>
<td>RAG2</td>
<td>T-</td>
<td>B-</td>
<td>NK+</td>
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<tr>
<td>ARTEMIS</td>
<td>T-</td>
<td>B+</td>
<td>NK+</td>
</tr>
<tr>
<td>ADA</td>
<td>T-</td>
<td>B-</td>
<td>NK-</td>
</tr>
<tr>
<td>Reticular Dysgenesis</td>
<td>T-</td>
<td>B+</td>
<td>NK+</td>
</tr>
<tr>
<td>SCID, multiple bowel atresias</td>
<td>T-</td>
<td>B+/-</td>
<td>NK+</td>
</tr>
<tr>
<td>SCID, congenital abnormalities</td>
<td>T-</td>
<td>B+/-</td>
<td>NK+</td>
</tr>
<tr>
<td>Severe DiGeorge Syndrome</td>
<td>T-</td>
<td>B+/-</td>
<td>NK+</td>
</tr>
<tr>
<td>CD3 Deficiency</td>
<td>T+/-</td>
<td>B+</td>
<td>NK+</td>
</tr>
<tr>
<td>CD8 Deficiency</td>
<td>T+/-</td>
<td>B+</td>
<td>NK+</td>
</tr>
<tr>
<td>Severe Ataxia Telangiectasia</td>
<td>T+/-</td>
<td>B+/-</td>
<td>NK+</td>
</tr>
<tr>
<td>Unknown genetic defect: ~5-25%</td>
<td>?</td>
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</table>
SCID - Summary

- Infections in the first year of life:
  - Recurrent bacterial, viral, and fungal infections
  - Severe infections (sepsis, meningitis)
  - Opportunistic pathogens (PJP pneumonia, CMV)
- Failure to thrive, chronic diarrhea
- Decreased ALC in most (< 2500/mm3 in infants)
- Naïve T cells decreased/absent
- Incidence unknown: estimates 1:50,000
- 100% fatal without early diagnosis and treatment
- Early diagnosis crucial
SCID - Diagnosis

1. Evaluate T cell QUANTITY:
   - CBC/Differential
   - Quantify T/B/NK cells by flow cytometry
   - TREC analysis

2. Evaluate T cell FUNCTION:
   - T cell proliferation after growth stimulation
   - Immune responses to vaccines

3. GENETICS
Complete Blood Count (CBC)

- Lymphocyte Count <2000/mm³ under 1 y/o is suspicious

184K

37.2

87N, 5L, 5M, 3B

184K

37.2

7.6K

ANC = 6,612/mm³

ALC = 380/mm³
Tagging Cells for Flow Cytometry

- Plasma
- Red Blood Cells

Macrophages  B Cells  T Cells
Flow Cytometry

Cells

Detector

Laser

Counter

Fluorescence (T Cells)
T cell Receptor Excision Circles (TREC)

Chromosome

TCRα

TCRδ

TCRα

Rearranged TCRα

Chromosome

Naïve T Cell

I

II

III

IV

TREC
Wisconsin was the first state to pilot a newborn screening program for SCID using Guthrie cards (2008).

There is no standard method used in all states for screening protocols.

Positives screens have a confirmatory panel done by flow cytometry: absolute T cell count (CD3) ± percentage of naïve T cell markers (CD4CD45RA)

Clinical Laboratory Standards Institute NBS06-A “Newborn Blood Spot Screening for Severe Combined Immunodeficiency by Measurement of T-cell Receptor Excision Circles; Approved Guideline, April 2013
Wisconsin Data First Three Years

207,696 infants screened

Abnormal TREC
- 72

Normal Flow
- 38

Secondary TCL
- 19

Abnormal Flow
- 33

Reversible
- 5

DiGeorge
- 4

SCID/sTCL
- 14
Other Associations: Abnormal TREC Screens*

* Conditions associated with T cell lymphopenia

- Prematurity
- Abnormalities of lymphatics (chylothorax, chyloperitoneum)
- Chromosomal abnormalities (eg trisomy21)
- Presumed metabolic disorders/NOS
- Multiple congenital anomalies/NOS
- Congenital heart defects, HLHS, cardiac surgery
- CHARGE syndrome
- Ataxia telangiectasia
- Hydrops, anasarca, third-spacing
- GI malformations including gastroschisis
- Neonatal leukemia
- Degenerative neuromuscular disorders/NOS
Resources from the IDF

IMMUNE DEFICIENCY FOUNDATION

www.primaryimmune.org ➔ “Quick Links”

SCID Newborn Screening Campaign
IDF Newborn Screening Toolkit
Available Pamphlets

Immune Deficiency (SCID)

For additional information and references please contact IDF
40 West Chesapeake Avenue, Suite 908
Towson, MD 21204
800-236-4433
410-321-6647
410-321-9165 (Fax)
www.primaryimmune.org
idf@primaryimmune.org

This brochure was developed with support from the New York - Mid-Atlantic Consortium for Genetic and Newborn Screening Services, the IDF SCID Initiative and SCID, Angels for Life Foundation,

experience.

Seattle Children's Hospital • Research • Foundation
SCID - Treatment

- **Immediate:**
  - Treat (or prevent) any infections
  - Start IVIG (antibody replacement)
  - Start prophylactic antimicrobials

- **Initiate Curative Therapy:**
  - Bone Marrow Transplantation (BMT)
  - Gene Therapy
Prophylaxis Prior to Definitive Therapy

- No live viral vaccines (rotavirus, MMR, varicella, FluMist)
- All blood products must be irradiated and leukodepleted (prevents GVHD and CMV transmission)
- Start regular IVIG or subcutaneous immunoglobulin (Hizentra) replacement therapy
- Pneumocystis prophylaxis (PJP) – start TMP/SMX at diagnosis or at 1 month of age
- No day care, avoid public places, limit contact with young children
- Do not breastfeed if mother is CMV positive
<table>
<thead>
<tr>
<th>Malignant</th>
<th>Nonmalignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Leukemias</td>
<td>• Aplastic Anemia</td>
</tr>
<tr>
<td>• Lymphomas</td>
<td>• Metabolic Diseases</td>
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<tr>
<td>• Myeloma</td>
<td>• Sickle Cell Disease</td>
</tr>
<tr>
<td>• Myelodysplasia</td>
<td>• Severe Immune Deficiencies</td>
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</tbody>
</table>
Transplant for SCID

- **Clinical Features:**
  - Life threatening Infections
  - Hematologic malignancy
  - Autoimmune disorders

- **Goal of BMT:**
  - Restore Immunity
    - T-cell number and function
    - B-cell number and function
    - Phagocytic function
  - Prevent hematologic malignancy
  - Prevent/correct autoimmune disorders
Background

Without definitive treatment patients with SCID do not survive.

Allogeneic bone marrow transplant is curative (gene therapy for some forms of SCID is in clinical trials).

Myeloablative regimens ("standard chemo")
- Infections/end organ dysfunction increase risk
- Neonates metabolize medications differently

Less intensive regimens are now in widespread use.
Unique Challenges of SCID Patients

- Patients typically present with severe life-threatening infections (pre-NBS)
- Partial replacement of the bone marrow can be sufficient to cure disease ("mixed chimerism")
- The disorder or genetic defect may dictate the transplant approach
- A multidisciplinary team with experts in these diseases is essential to optimize outcome
Outcomes: Early vs. Late Treatment

46 SCID infants with transplant at than 3.5 months of age or less

113 SCID infants with transplant at greater than 3.5 months of age

Summary: SCID Meets NBS Criteria

- Prevalence of the disease 1:100,000 or greater
  - SCID: about 1:50,000 (based on NBS data so far)
- Can the disorder be detected by routine physical exam?
  - SCID: No, baby generally appears normal at birth
- Does the disease cause serious medical complications?
  - SCID: Virtually 100% fatal within the first year of life
- Is there a cheap, sensitive and specific screening test?
  - SCID: Real time PCR to enumerate TRECs ($8/test)
- Is there a confirmatory test?
  - SCID: Lymphocyte subset analysis (flow cytometry)
- Does early detection improve outcome?
  - SCID: Marked improvement in outcome after BMT or gene therapy (curative therapy)
The Ultimate Goal – Cure!!

Thanks!