Newborn Screening for Severe Combined Immune Deficiency Syndromes (SCIDS): Why; why now?

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No financial conflicts of interest relevant to today's topic
But I'm working on one!
Member of state advisory panel of consulting immunologists for SCIDS NBS program

Disclosures

Learning objectives

- Review clinical presentation and underlying genetic basis of SCIDS
- Recognize the need for a newborn screening (NBS) program for SCIDS
- Understand the primary care provider's role in the SCIDS NBS program

SCIDS: Definition

- Severe
  - Fatal if untreated
- Combined
  - Reduced numbers and/or function of both T and B cells
- Immune Deficiency
  - Very reduced or absent immune function
  - Opportunistic and other serious infections
- Syndromes
  - Multiple genetic defects

SCIDS: Facts

- Rare, est. 1 in 50,000-500,000 births
- 3:1 males:females
- Life expectancy averages <2-3 years
- Highly curable with stem cell transplant and/or gene therapy

“...SCID is a pediatric emergency. The average age at diagnosis is 6 1/2 months. If affected infants survive this long without a serious infection, they may be readily resuced with bone marrow transplantation...Once an infant is seriously infected, it becomes difficult, if not impossible, to intervene successfully. Thus it is of overriding importance to make the diagnosis of SCID early.”

F. Rosen, J Peds, 1997
Clinical Presentations

- Opportunistic infections
  - CMV retinitis
  - Pneumocystis jiroveci pneumonia
  - Viral pneumonia
- Oral thrush
- Skin rash
- Potentially due to maternal engrafted T cells
- Failure-to-thrive
- +/- diarrhea
- Family history

Laboratory clues to SCIDS

- Lymphopenia
  - Especially lack of T cells
  - B and NK cells may be decreased, normal or increased
- Lack of thymus on x-ray
- Hypogammaglobulinemia
- Decreased production
- Increased consumption

Lymphopenia

- Cutoff value higher in children due to relative lymphocytosis
- Values below 3,000/mm³ suspicious
- Follow-up with T cell marker studies
- HIV confirmation on baby and/or mother if CD4 low

Mitogen responsiveness in SCIDS

Summary-Early Diagnosis

- Beware pneumonia that doesn’t clear
- Thrush, diarrhea, rash
- Ask about family history, siblings, consanguinity, etc.
- Look carefully at CBC for lymphopenia
- Get T & B cell markers
- Call your local immunologist!
**SCIDS Gene Defects**

<table>
<thead>
<tr>
<th>Flow pattern</th>
<th>Gene defect</th>
<th>Inheritance</th>
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<tbody>
<tr>
<td>T-B+NK-</td>
<td>IL2RG</td>
<td>X-linked AR</td>
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<tr>
<td></td>
<td>Jak3, IL7RA</td>
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<tr>
<td>T-B+NK+</td>
<td>CD45, CD3δ/ε, IL7RA</td>
<td>AR</td>
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<tr>
<td>T-B-NK-</td>
<td>ADA</td>
<td>AR</td>
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<tr>
<td>T-B-NK+</td>
<td>RAG-1, -2</td>
<td>AR</td>
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<td></td>
<td>Artemis</td>
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**Distribution of SCIDS subtypes**

- Jak3: 15%
- ADA: 7%
- XSCID: 5%
- Miscellaneous: 33%
- Unknown: 15%

**Recent case study**

- Valentina, 7 mo. old female from LRGV
- Hospitalized in three consecutive months for “RAD” vs. viral pneumonia; impending respiratory failure
- Failure to thrive
- BAL-P. jirovecii
- RAG-1 gene mutation
- Mother’s question: “Dr. Infante, can't they do newborn screening for SCIDS?”
- Survivor, UCBT

**Secretary's Advisory Committee on Heritable Disorders in Newborns and Children Criteria**

- Disorder is medically serious
- Spectrum of disease well-characterized
- Prospective data from pilot screening
- Low rate of false negative results
- Patients likely to benefit from treatment can be identified
- Effective treatment can be given before symptoms begin

**Survival benefit from early treatment**

Buckley, JACI 2012
Immunological benefit of early treatment


Cost savings of early treatment

Buckley, JACI 2012

Pros and cons of various screening test methodologies

Puck, JACI 2012

Distribution of ALC and CD3 in SCIDS vs. normal newborns

Buckley, JACI 2012

TRECs: T Cell Receptor Excision Circles

Puck, JACI 2012

TRECs performance from Guthrie cards

Puck, JACI 2012
Typical screening algorithm

Typical screening algorithm

Verbsky, et al. JACI 2012

SCIDS NBS Outcomes 2012

SCIDS NBS Outcomes 2012

Buckley, JACI 2012

Non-SCIDS causes of low TREC

- DiGeorge syndrome
- Other severe immunodeficiencies
- Ataxia-telangiectasia
- Trisomy 21
- Neonatal cardiac surgery with thymectomy
- Neonatal leukemia

Non-SCIDS causes of low TREC

Verbsky, et al. JACI 2012

Supportive and preventive measures

Supportive and preventive measures

Verbsky, et al. JACI 2012

Infection prophylaxis

Infection prophylaxis

Verbsky, et al. JACI 2012

TX SCIDS ACT Form

You should take the following actions:

- Contact family to inform them of the positive SCID screening results, ascertain clinical status, and refer to an immunologist.
- If the infant has any signs of illness, refer to a pediatric hospital right away for evaluation.
- Well infants may stay at home safely during preliminary diagnostic testing as they have some protection from maternal antibodies.
- Infants with congenital or neonatal infections should be immediately evaluated by an immunologist (see attached list).
- Avoid exposing patient to illness pending completion of testing.
- If the infant requires transfusion of any blood products, be sure that only leukoreduced, irradiated products that are negative for cytomegalovirus (CMV) are used.
- The primary care physician should obtain an MRI with differential and T and B cell lymphopenia.
- Do not give live attenuated rotavirus vaccine, which could cause serious diarrhea in a baby with SCID. This vaccine is to be given only after an immunology specialist confirms that the baby's immune system is normal.
- Consult with a specialist in pediatric immunodeficiency disease(s) (a pediatric immunologist) who will assist with further testing.
- Provide the family with basic information about SCID and T cell lymphopenia.
- Repeat newborn screen if second screen has not been done.
Definitive Treatment

- Hematopoietic stem cell transplant
- Current treatment of choice
- Gene therapy
  - Coming soon to a hospital near you?

Effect of HLA match on outcome


SCIDS gene therapy prospects

- Single gene defects, known
- Constitutive gene expression in many cases
- Accessible precursor cells, i.e. HSCs
- Corrected cells have growth advantage

X-SCIDS Gene Therapy

- Subjects lacking HLA-matched sibling
- Marrow harvest, CD34 selection
- In vitro transfection with defective retrovirus
- No short-term adverse effects

Follow up results

- 10 children treated in between 1999-2002
- 9 had evidence of gene-corrected T and NK cells
- 7 had normalized T cell counts
- 9/10 alive
- 4/10 T cell leukemia; one died
- Additional trials with self-inactivating vectors (SIV) underway
  
  Hacein-Bey-Albina, et al. NEJM 2010

Take home message

- SCIDS is a pediatric emergency
- SCIDS can be detected by newborn screening
- SCIDS can be effectively treated
- Together, PCPs and pediatric immunologists can make excellent outcomes a reality

We Can Do It!
Key references


THANK YOU!

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