Newborn screening for immune deficiency disorders: what have we learned so far?

Anthony J. Infante, MD, PhD
Professor, Pediatrics (Immunology & infectious diseases) and Microbiology & Immunology, UTHSCSA

Learning objectives

- Review the rationale for implementation of newborn screening for SCIDS
- Summarize the results of adding SCIDS to state newborn screening (NBS) panels
- Discuss whether newborn screening for other immune deficiency disorders may be warranted

Case 1

- 7 mo. old boy, recently emigrated from India, parents contracted to work at large local business
- Presented to ER with fever, deltoid abscess, axillary lymphadenopathy
- Returned to ER with inability to bear weight on left leg

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>ALC: 216 cells/mm³</td>
</tr>
<tr>
<td></td>
<td>CD8: 6 cells/mm³; CD4: 7; CD8: 0; CD4/8: 0.62</td>
</tr>
<tr>
<td>WBC</td>
<td>Negative</td>
</tr>
<tr>
<td>CSF</td>
<td>IgA undetectable, IgM undetectable, IgG 141 mg/dl</td>
</tr>
<tr>
<td></td>
<td>83 WBCs/mm³; 50% PMNs, 43% MNCs; 2% L; protein 48 mg/dl; glucose 69 mg/dl</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>Normal: 8 mm lesion in right cerebral peduncle; prominent abnormal T2 weighted signal at cord T1 level on the left; additional abnormal signal and contrast enhancement of several nerve roots</td>
</tr>
<tr>
<td>MRI</td>
<td>Enlarged lymph nodes: left supravacuicular, left axilla, retroperitoneal</td>
</tr>
</tbody>
</table>

Disclosures

- No connections with commercial ventures relevant to this topic
- Consulting Immunologist, Texas DSHS Newborn Screening Programs
MRI

Microbiology

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>No bacterial growth at all hrs.; later positive for AFB identified as M. bovis/BCG</td>
</tr>
<tr>
<td>CSF</td>
<td>Negative bacterial meningitis screen and gram stain; negative fungal smear and culture; negative PCR for HSV-1 and 2, CMV</td>
</tr>
<tr>
<td>Blood</td>
<td>Enterovirus isolated; identified as iVDPV1</td>
</tr>
<tr>
<td>Lymph nodes FNA</td>
<td>AFB stain positive; identified as M. bovis/BCG</td>
</tr>
</tbody>
</table>

Case 1

- Genetic diagnosis of RAG-1 deficient SCIDS
- Vaccine-associated paralytic polio (VAPP)
- BGG-osis
- Family history of consanguinity and early infant death
- After meeting with several consultants and ethics committee, parents decided to withdraw life support
- India declared free of endemic polio in 2012; can expect VDPP cases with continued OPV use

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

Clinical Presentations

- Opportunistic infections
  - CMV retinitis
  - Pneumocystis jiroveci pneumonia
  - Viral pneumonia
  - Infections derived from live viral vaccines
- Oral thrush
- Skin rash
- Potentially due to maternal engrafted T cells
- Failure-to-thrive
  - +/- diarrhea
- Family history
Definitive Diagnosis

- Clinical history, especially opportunistic infection
- Lymphocyte subsets by flow cytometry
  - Low or absent T cells (typically <300)
- Genetic analysis for candidate gene mutations

Survival benefit from early treatment

Impact of age largely a result of pre-existing infections

Cost savings of early treatment

Newborn screening options for SCIDS

- CBC and diff
- Flow cytometry
- PCR & sequencing of candidate genes
  - More than a dozen at last count
- RT-PCR for TREC
  - Byproduct of TCR gene rearrangement
  - Stable, episomal DNA
  - Absent or reduced in most genetic forms of SCIDS
Results

- Infants born from January 2008 through July 2013 were included. Representatives from 15 states plus the Navajo Area Indian Health Service contributed data from 3,030,083 newborns screened with a TREC test.
- Screening detected 52 cases of typical SCID, leaky SCID, and Omenn syndrome, affecting 1 in 58,000 infants (95% CI, 1/46,000-1/80,000).
- Survival of SCID-affected infants through their diagnosis and immune reconstitution was 87% (45/52), 92% (45/49) for infants who received transplantation, enzyme replacement, and/or gene therapy.

Newborn Screening for Severe Combined Immunodeficiency in Screening Programs in the United States

<table>
<thead>
<tr>
<th>State</th>
<th>Cases Detected</th>
<th>Cases Verified</th>
<th>Cases Excluded</th>
<th>Total Screened</th>
<th>Positive Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NY</td>
<td>12</td>
<td>12</td>
<td>0</td>
<td>1,212,000</td>
<td>1.0% (0.98%, 1.02%)</td>
</tr>
<tr>
<td>CA</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>1,000,000</td>
<td>1.0% (0.98%, 1.02%)</td>
</tr>
<tr>
<td>TX</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>800,000</td>
<td>1.0% (0.98%, 1.02%)</td>
</tr>
<tr>
<td>WA</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>600,000</td>
<td>1.0% (0.98%, 1.02%)</td>
</tr>
<tr>
<td>FL</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>500,000</td>
<td>1.0% (0.98%, 1.02%)</td>
</tr>
<tr>
<td>MA</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>400,000</td>
<td>1.0% (0.98%, 1.02%)</td>
</tr>
<tr>
<td>GA</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>300,000</td>
<td>1.0% (0.98%, 1.02%)</td>
</tr>
<tr>
<td>CO</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>200,000</td>
<td>1.0% (0.98%, 1.02%)</td>
</tr>
<tr>
<td>NV</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>100,000</td>
<td>1.0% (0.98%, 1.02%)</td>
</tr>
</tbody>
</table>

The table shows the number of cases detected, verified, and excluded from screening programs in the United States, with the percentage of positive cases (95% CI) for each state.

DOI:10.1001/jama.2014.9132
SCIDS is about twice as frequent as previously estimated (guessed)

TRECs forms the basis for robust NBS

No subsequent SCIDS cases diagnosed in states implementing screening

Screening allows realization of expected survival advantage of early detection

Conclusions

10 month old boy transferred for neuro rehab

PMH

S. pneumoniae meningitis age 4 mos., recovered

S. pneumoniae meningitis age 9 mos., devastated

Immunizations up-to-date

Hypogammaglobulinemia noted

Very low B cells in blood

BTK mutation detected

Dx: X-linked agammaglobulinemia (XLA)

Quantitative Immunoglobulins

IgG: 115 mg/dl (130-170)

IgA: <1.0 mg/dl (1.0-6.0)

IgM: <1.0 mg/dl (1.0-4.0)

Flow Cytometry

WBC: 10 6-17 10^9/mm^3

Lymph: 34.7 (L) 44-74%

CD3: 90.95 (H) 53-82%

CD3#: 3100 (L) 3600-4600/mm^3

CD3/8#: 19.2 8-31

CD3/4#: 2350 (L) 2600-3500/mm^3

CD3/8#: 655 350-1500/mm^3

CD4:CD8 Ratio: 3.59 0.9-3.6

CD16+56#: 243 21-560/mm^3

CD19#: 7 (L) 11-45]%

Effects of vaccination

A Devastating Outcome in Undiagnosed X-Linked Agammaglobulinemia— A Call for Earlier Screening

Karen E. Bruner, MD1, Anthony J. Infante, MD, PhD2

1 Wilford Hall Ambulatory Surgical Center, Joint Base San Antonio, University of Texas Health Sciences Center San Antonio

Trainee poster award, 2nd place, ACAI, 2014

Severe bacterial infections (pneumonia, sepsis, meningitis, osteomyelitis)…may occur in a normal child, a second occurrence should alert the physician to possible immunodeficiency." Conley & Steffen, Immunologic Disorders in Infants & Children, 4th edition, 1996.
Delay in diagnosis common in XLA

- 254 subjects (131 males) median age 4.5 years
- Screened for hypogammaglobulinemia
- 2 boys found to have genetically confirmed XLA
- Proposal: screen all boys <5 yo with CAP


NBS for XLA?

- Avoid rare but devastating outcomes
- Prevent bronchiectasis
- Reduce hospitalizations for CAP?

Techniques for NBS in XLA

- Ig levels
- Flow cytometry
- Candidate gene mutation analysis
- RT-PCR based assay

KRECs: B cell equivalent of TREC
Multiplex RT-PCR for TREC and KREC

Summary
- Statewide newborn screening has been successfully implemented for SCIDS
- Expected results of early SCIDS detection appear to be realized
- XLA can have adverse consequences when diagnosis is delayed
- Newborn screening for XLA is feasible and may be warranted

References
- SCIDS Polio
  - Trimble, et al. MMWR Weekly 2014; 63(33):721-724
- SCIDS NBS
  - Kwan, et al. JAMA 2014; 312(7):729-738
- SCIDS BMT outcomes
- XLA in CAP
- NBS for T & B disorders

Clinic referrals
- Immune deficiency, incl. newborn screen evals
  - University Hospital Pediatrics Hematology/Oncology & Infusion Center, 10th floor, Horizon Tower, 358-2590
- Rheumatology
  - UHS Robert B. Green Clinic, 6th floor, 358-KIDS (5437)
- UTHSCSA Office
  - 567-5250