Are You Ready to Follow Up Abnormal Newborn Screening for Metabolic Disorders

Hong Li, MD, PhD
Assistant Professor
Department of Human Genetics and Pediatrics
Emory University, School of Medicine
3/11/2017

Learning Objectives

• Familiar with Newborn Screening workflow in Georgia

• Understand the important roles of primary care physicians in NBS follow up process

• Provide useful web-based resources for NBS follow up

• No disclosure
Why do you need to know rare metabolic diseases?

- Individually—rare; Collectively—common (~1/1000)
  - NBS screens >50 IEMs

- Can be life-threatening!

- Many of them are treatable.

DO NOT MISS TREATABLE DISEASE!!!

Georgia Newborn Screening

Approximate Births 130,946 (NCHS data, 2014)

Timeline of metabolic NBS in Georgia

- 1968: Started NBS for PKU via BIA
- 1978: Added another 4 metabolic diseases
  - Homocystinuria
  - Maple syrup urine disease
  - Tyrosinemia
  - Galactosemia
- 2003: Biotinidase Deficiency (enzyme assay)
- 2007: Expanded metabolic NBS by using MS/MS
  - 29 Core Conditions Recommended for Screening
  - 25 Additional Conditions for which test results should be reported.
**What to screen?**

**Core Metabolic diseases by MS/MS**
- 3-Methylcrotonyl-CoA Carboxylase Deficiency (MCADD)
- Methylmalonic Acidemia (MMOA)
- Phenylketonuria (PKU)
- Propionic Acidemia
- Trifunctional Protein Deficiency
- Tyrosinemia
- Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)
- Congenital Adrenal Hyperplasia
- Cystic Fibrosis
- Sickle Cell Disease and other hemoglobin conditions
- Hypothyroidism
- SCID
- Hearing
- Critical Congenital Heart Disease

**Others**
- Galactosemia
- 3-Methylcrotonyl-CoA Carboxylase Deficiency (3-MCC)
- Argininosuccinic Aciduria
- Beta-Ketothiolase Deficiency
- Carnitine Uptake Defect
- Citrullinemia
- Carnitine Uptake Defect
- 3-OH 3-CH3 Glutaric Aciduria (HMG)
- Carnitine Uptake Defect
- Cystinemia
- 3-OH 3-CH3 Glutaric Aciduria (HMG)
- Homocystinuria
- Isovaleric Acidemia
- Citrullinemia
- Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)
- Maple Syrup Urine Disease (MSUD)
- Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)
- Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)
- Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)
- Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)
- Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)
- Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)

**When to screen?**

- Required by law on ALL newborns
- Collect specimen between 24 hours and 7 days of life, **ideally 24-72 hours**
  - If too early, lack of enough protein exposure, can cause false negative
  - If too late, patient can be symptomatic before result is not available
- A second test is required if initial screen is done prior to 24 hours

**The Challenge of NICU Babies**

- Georgia has adopted new guidelines for screening NICU babies
  - Collect 1st specimen **on admission**
  - Collect 2nd between 48 and 72 hours of life
  - Collect 3rd at 28 days of discharge
**What is Newborn Screening?**

- Six part public health program designed to prevent severe and lethal outcomes from a variety of congenital disorders
  - Education: Family and Providers
  - Screening
  - Follow-up (short and long term)
  - Evaluation
  - Diagnosis
  - Management

**NBS Follow up is a process**

1. Triage results
2. Assess patient
3. Recommendation
4. Referral

**Triage positive results**

- To decide how important the result is
  - Specific follow-up protocols
  - Region 4 Stork (R4S) project risk calculator: estimate LOW, MEDIUM and HIGH risk

- To better communicate with PCP
  - Borderline Abnormal: Passive Follow-Up
  - Routine Abnormal: Active Follow-Up
  - Critical Abnormal: Super Active (Critical) Follow up
Children's Healthcare of Atlanta | Emory University

**Basic Principle of Inborn Errors**

- **A** ENZYME
- **B**
- Effects of too little B

Toxic Effects (acute or chronic) of A And its byproducts

A/B ratio: elevated

---

**Phenylketonuria (PKU)**

- Autosomal Recessive
- 1/10,000 (carrier frequency 1/50)
- False Positives due to TPN
- Chronic neurologic toxicity
- NO ACUTE SYMPTOMS IN NEWBORN (except maybe mousy odor).
- Rx : Low Phenylalanine Diet
  - BH4-Kuvan
  - PEG-PAL (Phase 3)

Screen:
- Phenylalanine level
- Phe/Tyr ratio

---

**Case 1**

NBS collected at 25 hours of life

- Phe 284.5umol/L (cut off < 160 umol/L)
- Phe/Tyr 7.37 (cut off < 1.4)
Evaluating Risk Using R4S

R4S score 144—medium risk

Children's Healthcare of Atlanta | Emory University

Georgia Newborn Screening Program Follow-up
Flowchart for Phenylketonuria (PKU) (<10 Days of Age at Collection)

WNL: Phe < 160 µM
WNL: Phe/Tyr < 1.4

GPHL performs MS/MS
Use Region 4 Calculator for PKU

Score is in the lowest risk category
Score is in a medium risk category
Score is in the highest risk category

If no s/s ("mousy" odor), repeat NBS
If no s/s and on TPN, repeat NBS 3 days after TPN is D/C

Proceed with confirmatory testing
Immediate metabolic consultation
Consult metabolic team, put MD in touch with dieticians

Confirmatory test: Plasma amino acid

<table>
<thead>
<tr>
<th>AMINO ACID</th>
<th>ANALYSIS</th>
<th>Method: Ion Exchange Chromatography</th>
<th>Normal</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taurine</td>
<td>&lt;130 mL</td>
<td>19 - 270</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arginine</td>
<td>&lt;80 mL</td>
<td>0 - 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ornithine</td>
<td>&gt;50 mL</td>
<td>12 - 25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valine</td>
<td>&lt;90 mL</td>
<td>0 - 65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycine</td>
<td>&lt;200 mL</td>
<td>12 - 65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate</td>
<td>&lt;70 mL</td>
<td>0 - 52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutamate</td>
<td>&lt;50 mL</td>
<td>0 - 40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tryptophan</td>
<td>&lt;40 mL</td>
<td>0 - 75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>&lt;100 mL</td>
<td>0 - 175</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Children's Healthcare of Atlanta | Emory University
Triage Categories

• Active Follow Up (Routine Abnormal)
  – Call providers to report results and check clinical status
  – Fax them results with recommendations
  – call families if necessary

Case 2

6 days old Boy

<table>
<thead>
<tr>
<th>Age of Collection</th>
<th>1 day, 16 hours old (1-7d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight</td>
<td>2160 gm</td>
</tr>
<tr>
<td>Ponderal-Glucosemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>GALT ENZYME</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age of Collection</th>
<th>1 day, 16 hours old (1-7d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight</td>
<td>2160 gm</td>
</tr>
<tr>
<td>Ponderal-Glucosemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>GALT ENZYME</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

Galactosemia screening-Enzyme assay

Galactose

Galactokinase

Galactose-1-phosphate

Galactose-1-Phosphate Transferase (GALT)

Galactose-1-phosphate

Tier 2: Total galactose

Tier 1: GALT enzyme
On 7/1/2016, you received a 2-page fax for

Abnormal NBS screening: Galactosemia

Triage Categories

- Passive Follow Up (Borderline abnormal)
  - Send a fax to the provider with the results, recommendations for assessment and to repeat the NBS
  - Send a letter to the family – bring this to your pediatrician
- Common metabolic cases:
  - Galactosemia
  - NICU baby on TPN
  - Unsatisfied card
Case 3

5 days old Boy

<table>
<thead>
<tr>
<th>Age at Indications</th>
<th>1 day, 3 month old [RPE]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight</td>
<td>3350 g</td>
</tr>
</tbody>
</table>

Possible MSUD

<table>
<thead>
<tr>
<th></th>
<th>Urea</th>
<th>1ket</th>
<th>3ket</th>
<th>1-methylketone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>50.8</td>
<td>155</td>
<td>405</td>
<td></td>
</tr>
<tr>
<td>RE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

R4S risk score:

314-High risk
For MSUD

Maple Syrup Urine Disease

• AR
• Brain edema
• Encephalopathy
• Maple Syrup odor (ear wax and urine)
• Rx:
  – Diet vs Hemodialysis

When a baby decides to hide

• We go on the proverbial “Wild Goose Chase”
  – Use internet searches
  – Use health related databases (GRITS)
  – Call the health department, WIC
  – Call the police

Courtesy From Angela, Wittenauer
Confirmatory test: Plasma amino acid

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arginine</td>
<td>9 - 35 µmol/L</td>
</tr>
<tr>
<td>Threonine</td>
<td>144 - 274 µmol/L</td>
</tr>
<tr>
<td>histidine</td>
<td>20 - 60 µmol/L</td>
</tr>
<tr>
<td>Histidine</td>
<td>104 - 384 µmol/L</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>52 - 126 µmol/L</td>
</tr>
<tr>
<td>Leucine</td>
<td>144 - 384 µmol/L</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>48 - 148 µmol/L</td>
</tr>
<tr>
<td>Valine</td>
<td>68 - 208 µmol/L</td>
</tr>
<tr>
<td>Methionine</td>
<td>12 - 55 µmol/L</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>40 - 145 µmol/L</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>29 - 129 µmol/L</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>28 - 78 µmol/L</td>
</tr>
<tr>
<td>Pyrimidines</td>
<td>0 - 5 µmol/L</td>
</tr>
<tr>
<td>Hydroxyproline</td>
<td>0.1 - 0.6 µmol/L</td>
</tr>
<tr>
<td>Proline</td>
<td>18 - 46 µmol/L</td>
</tr>
<tr>
<td>Alanine</td>
<td>334 - 0 µmol/L</td>
</tr>
</tbody>
</table>

Triage Categories

- Critical Follow Up
  - Call providers to report results and check clinical status
  - Fax them results with recommendations
  - Find the baby
    - Police or health departments
  - Seen in diseases with life-threatening risk
    - Some organic aciduria,
    - Urea cycle diseases,
    - MSUD

Case 4

- AZ is a 9 days old girl, who was sent to ER due to poor feeding and respiratory failure required intubation
  - Hypoglycemia 37
  - Metabolic acidosis: CO₂=5
  - Hyperammonia: 340µmol/L
  - Seizure

Where is NBS result?
Case 4

**Assess patient is critical!!!**

- Elevated C3
- Metabolic acidosis
- Hyperammonemia
- Hypoglycemia
- Encephalopathy
- MMA and (PA)
- Cobalamin defects
- Maternal B12 deficiency

**Metabolic defects causing elevated C3**

- Methylmalonyl-CoA
- Succinyl-CoA
- Propionyl CoA
- Metabolism
- Homocysteine
- Methionine
- Cbl A, B
- Cbl C, D
- Cbl E, G
- Met synthase
- Mut/Ch A, B
- MMA
- PA

Propanoic acidemia risk score=52 — medium risk
Cbl C, D risk score=165 — high risk
MUT/Ch A, B risk score=100 — high risk

**Age of Collection**

<table>
<thead>
<tr>
<th>Value</th>
<th>M</th>
<th>D</th>
<th>O</th>
<th>L</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3</td>
<td>6.36</td>
<td>6.2</td>
<td>8.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3 / C2</td>
<td>5.18</td>
<td>5.12</td>
<td>6.27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case 4

- Reported to PCP on Day 5
- Recommended to immediately assess baby for:
  - poor feeding, vomiting, hypotonia, lethargy, tachypnea
  - PCP reported: saw patient earlier the day, “doing well” + "breastmilk feeding" + "adding formula" due to latching difficulty
  - But mother reported she concerned baby’s feeding even before discharged and nurse reassured her then, after discharged, she still not feeding well on BM, lost significant weight, then tried to add formula
- Recommended to send confirmatory tests
  - collected Day 6 (weekend)
- Over the weekend, worsening poor feeding, respiratory distress, can not reach PCP, sent to ER on day 9

What did we learn from it?

- Re-assess signs and symptoms is very important
- Close management of feeding difficulties is essential for all neonates awaiting NBS results
- Educate caregiver to watch the signs and symptoms and ensure they can reach physician or office staff to discuss if presents with
  - poor feeding, vomiting, hypotonia, lethargy, tachypnea
- Contact us for any questions

Morbidity and mortality among exclusively breastfed neonates with medium-chain acyl-CoA dehydrogenase deficiency

Several maternal metabolic diseases can be detected through positive NBS

- Maternal B12 deficiency
  - Is mom vegan or vegetarian?
  - Is mom B12 deficient, any history of anemia?
  - Has mom had gastric bypass or any other chronic GI Dz?
  - What is baby eating?
- 3-methylcrotonyl-CoA carboxylase (3-MCC) deficiency
- Carnitine uptake defect

Collect maternal sample at the same time is also important!

**HOW MUCH BLOOD????**

Plasma amino acids (GREEN TOP)  
200 µL plasma (0.4 cc blood)

Acyl carnitine profile (GREEN TOP)  
20 µL plasma (0.04 cc)

Carnitine profile 20 µL plasma (0.04 cc)  
(GREEN TOP)

Plasma MMA (GREEN TOP)  
50 µL plasma (0.1 cc)

Plasma homocysteine (Purple Top)  
100 µL plasma (0.2 cc)

2 cc should cover almost all labs
Case 5

- 3yo boy presented to ER with poor feeding, vomiting for one day, progressive lethargy and mental status change, no fever.

Lab

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>135</td>
<td>102</td>
<td>28</td>
<td>79</td>
<td>9.8</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>0.4</td>
<td>12.5</td>
<td>36.4</td>
</tr>
<tr>
<td>189</td>
<td>N59 L38</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ammonia 356 umol/L (9-50 umol/L)

NBS: Normal

Urea Cycle Disorders

Plasma amino acids
NBS does not include all IEMs

- Proximal UCDs
- Low excreter Glutaric aciduria-type I
- Tyrosinemia Type I
- B6 responder homocystinuria
- Intermittent MSUD
- Glycogen storage disease/gluconeogenesis
- Organelle diseases (Mito, LSD, Peroxisome Dz...)

Case 6

7yo F with NBS identified MCADD, being lost for follow up since infancy and managed by PCP. Admitted to ICU due to
- Mental status change
- Hypoglycemia 41
- Metabolic acidosis
- Leg weakness/cramp (CK 6000)
- Tachycardia
- Hepatomegaly-fatty liver with mild fibrosis

After almost 20hrs “fasting” at a sleep-over party

Fatty acid oxidation (FAO) defect

- FAO represents a physiological response to tissue energy depletion when
  - fasting,
  - during febrile illness,
  - increased muscular activity.

- Can present with
  - rhabdomyolysis, myopathy (Muscle),
  - cardiomyopathy (Heart),
  - fatty liver (Liver)
What did we learn from it?

- **Team work** for long term follow up
  - Emphasize the follow up at metabolic center
    - Clinical presentation can be variable, requires individual treatment plan
    - False reassurance like this case
    - Can ignore the possibility of dual rare diagnosis
    - Most are autosomal recessive. 25% recurrent risk, if you know mother is pregnant again, ensure to notify us*
  - Coordinate follow up lab or sick lab locally
  - Immediately evaluate patient when sick (risk factors)
  - Page genetics on-call physician (24hours, 7days), if any question
    (404-785-7778, page genetics on-call)

Georgia Pilot Programs

Lysosomal Storage Disorders

- Pompe Disease
- Mucopolysaccharidosis I (MPS-1)

Pompe Disease

- AR disorder of α1,4-glucosidase
- Severe infantile form:
  - Dilated cardiomyopathy
  - FTT
  - Macroglossia
  - Hypotonia
- Diagnosis:
  - Assay enzyme in lymphocytes, DNA
- Enzyme Replacement Therapy available since April 2006.
MPS1

- Classic Lysosomal Storage Disease.
- Hurler, Hurler-Schei, Schei (Most severe> Mildest).
- Autosomal recessive defect in alpha-L-iduronidase that breaks down glycosaminoglycans
- Usually normal at birth, but develop:
  - Coarse facial features
  - Hepatosplenomegaly
  - Dysostosis multiplex
  - Corneal Clouding
- Early BMT (< 18 months) significantly improves morbidity and mortality

Pilot Programs - What will Happen?

- Results will NOT appear on screen
- If normal – NO notification
- If abnormal, NICU/PCP will be notified
- Emory follow-up team will guide you with follow-up testing 404-778-8560
- Costs will be covered for Pompe. Funding for MPS1, if child has no insurance or financial means.

Questions??
THANK YOU ALL!