Newborn Screening: False Positives and Negatives and Neonatal Cases

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Objectives

- Describe the expanded newborn screening (NBS) process from blood spot to diagnosis
- Explain several causes of false positives and false negatives on NBS
- Review cases of classical presentations of metabolic disease in the neonate
NBS

- 1960s: NBS for PKU
- 1999-2000s: expanded to ~29 disorders
- 2009: TX CF screening
- 2013: TX SCID screening
- 5/2015: TX metabolic secondary targets
- Future: ?Pompe disease, X-linked ALD, MPS 1
Texas NBS

- #1 24-48 hours old
- #2 7-14 days old
Electron Transport Chain

- Glucose → Pyruvic Acid
  - +2 ATP
  - Anaerobic Glycolysis

- Pyruvic Acid → Acetyl CoA
  - Aerobic Glycolysis

- Acetyl CoA → Krebs Cycle
  - +36 ATP
  - Aerobic Respiration

- Krebs Cycle → Amino Acids
- Amino Acids → Glucose
- Amino Acids → Fats
29 Core Disorders

- CAH
- Hypothyroidism
- Hemoglobinopathies (3)
- Galactosemia
- Biotinidase deficiency
- Cystic fibrosis
- PKU
- MSUD
- Homocystinuria
- Tyrosinemia type I
- Citrullinemia
- Argininosuccinic acidemia
- Isovaleric acidemia
- Glutaric acidemia type I
- HMG-CoA-lyase deficiency
- Multiple carboxylase deficiency
- MMA, mut 0
- MMA, cbl forms
- 3-MCC-deficiency
- Propionic acidemia
- Beta-ketothiolase deficiency
- MCAD deficiency
- VLCAD deficiency
- LCHAD deficiency
- Trifunctional protein deficiency
- Carnitine uptake deficiency
24 Secondary Disorders

- 8 amino acidopathies
- 8 fatty acid oxidation disorders
- 7 organic acidemias
- Additional hemoglobinopathies
- T-cell related lymphocyte defects
Inclusion on NBS

- ACMG criteria for selecting disorders
  - Can be identified at a phase (24-48 hours after birth) at which it would not ordinarily be detected clinically
  - A test is available with appropriate sensitivity and specificity
  - Demonstrated benefits of early detection, intervention, and treatment for the condition
Process at State Lab

- Receive and sort ~1500 first NBS and ~1200 repeat NBS daily
- Punch samples from cards
- Analysis (10+ different processes)
NBS Methods

- Tandem mass spectrometry (MS/MS)
  - Evaluates for disorders of fatty acid oxidation, amino acidopathies, and organic acidemias
  - 2-minute run per sample
- Enzyme studies – biotinidase, GALT
- Other – succinylacetone, Hb, TSH, CAH, CF, SCID
- DNA panels
NBS Methods

- Interpretation of results
  - All abnormal results are reanalyzed
- Turn-around time for an abnormal result
  - 3-5 days after receipt at lab
NBS Results

- **Borderline**
  - Faxed report will advise if repeat NBS or other testing is needed

- **Abnormal**
  - Phone call and faxed results to provider with list of metabolic specialists and ACT and FACT sheets for suspected disorder
Resources for Healthcare Providers

The Texas Department of State Health Services’ Newborn Screening (NBS) Program screens for 20 core conditions using blood spots. On May 26, 2015, NBS added screening and reporting on secondary conditions. View Fact Sheets for the 24 secondary conditions.

ACT Sheets

ACT Sheets or ACTion sheets are action plans for each disorder that provide recommended immediate next steps for a health professional to follow when a newborn has an out-of-range test result.

Amino Acid Disorders

Core: Argininosuccinic Acidemia (ASA), Citrullinemia (CIT), Homocystinuria (HCY), Maple Syrup Urine Disease (MSUD), Phenylketonuria (PKU), Tyrosinemia Type I (TYR I)

Secondary: Argininemia (ARG), Benign Hyperphenylalaninemia (H-PHE), Bioppterin Defect in Cofactor Biosynthesis (BIOPT-BS), Bioppterin Defect in Cofactor Regeneration (BIOPT-REG), Citrullinemia, type II (CIT II), Hypermethioninemia (MET), Tyrosinemia, type II (TYR II), Tyrosinemia, type III (TYR III)

Fatty Acid Oxidation Disorders

Core: Carnitine Uptake Defect (CUD), Long-chain L-3-OH acyl-CoA Dehydrogenase Deficiency (LCHAD), Medium-chain acyl-CoA dehydrogenase Deficiency (MCAD), Trifunctional Protein Deficiency (TFP), Very Long-chain acyl-CoA Dehydrogenase Deficiency (VLCH)

Secondary: 2,4 Dienoyl-CoA reductase deficiency (DE RED), 3-Hydroxyacyl-Coenzyme A Dehydrogenase Deficiency (HADH)

http://www.dshs.texas.gov/newborn/expandprofessional.shtm
Elevated C8 with Lesser Elevations of C6 and C10 Acylcarnitine

Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)

Differential Diagnosis: Medium-chain acyl-CoA dehydrogenase deficiency (MCADD), Medium-Chain ketoacyl-CoA Thiolase Deficiency (MCTD), MCT4

Condition Description: MCADD deficiency is a fatty acid oxidation (FAO) disorder. FAO occurs during prolonged fasting and/or periods of increased energy demands (fever, stress) when energy production relies increasingly on fat metabolism. In an FAO disorder, fatty acids and potentially toxic derivative carnitines become a deficiency in use of the mitochondrial FAO enzymes. MCT4 multiple analysis may be elevated.

Conditions associated with this analyte have been identified by the Society of Inherited Metabolic Disorders (SIMD) as critical, and require immediate action.

You Should Take the Following IMMEDIATE Actions:

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, and lethargy).
- Immediate telephone consultation with pediatric metabolic specialist (See attached list).
- Evaluate the newborn (poor feeding, lethargy, hypotonia, and hepatomegaly).
- If signs are present or infant is ill, initiate emergency treatment with IV glucose. Transport to hospital for further treatment in consultation with metabolic specialist.
- If infant is asymptomatic initiate timely confirmatory/diagnostic testing, as recommended by specialist.
- Initiate testing: Plasma acylcarnitine profile, plasma carnitine levels, urine acylcarnitines, and urine organic acids.
- Repeat newborn screen if the second screen has not been done.
- Educate family about need for infant to avoid fasting. Even if mildly ill, immediate treatment with IV glucose is needed.
- Report findings to newborn screening program.

Diagnostic Evaluation: Plasma acylcarnitine analysis will show characteristic pattern consistent with MCADD deficiency. Urine organic acid analysis may also show an abnormal profile. Diagnosis may be confirmed by mutation analysis of the MCADD gene. MCT4 is extremely rare.

Clinical Considerations: MCADD deficiency is usually asymptomatic in the newborn, although it can present acutely in the absence of hypoglycemia, metabolic acidosis, hypoketonaemia, and hyperammonemia. MCADD deficiency is associated with high mortality unless treated promptly. Milestone features include vomiting, lethargy, and hypotonic hypoglycemia. Untreated MCADD is a significant cause of sudden death. Acylcarnitines may normalize on the second screen in affected babies, therefore an infant with an out of range first newborn screen and normal second newborn screen will still need a metabolic evaluation.

Additional Information:
- American College of Medical Genetics and Genomics:
- Genetic Home Reference

STAR-G FELSI
- Participants - http://www.newbornscreening.info/Participants/Participants/MCADD.html
- Professionals - http://www.newbornscreening.info/Professionals/Professionals/MCADD.html

Disclaimer: This information is adapted from the American College of Medical Genetics and Genomics (ACMG) website. 01/2015
Newborn Screening FACT Sheet

Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCAD)

What is MCAD?
MCAD is a type of fatty acid oxidation disorder. People with MCAD have problems breaking down fat into energy for the body.

What Causes MCAD?
Enzymes help start chemical reactions in the body. MCAD happens when an enzyme called “medium chain acyl-CoA dehydrogenase” is either missing or not working. This enzyme breaks down certain fats in the food we eat into energy. It also breaks down fat already stored in the body.

What Symptoms or Problems Occur with MCAD?
(Symptoms are something out of the ordinary that a parent notices.)
MCAD can cause bouts of illness called Metabolic Crisis. Children with MCAD often show symptoms for the first time between 6 months and 2 years of age. Some of the first signs of a Metabolic Crisis are:
- too much sleepiness
- behavior changes (such as crying for no reason)
- irritable mood
- poor appetite
If a Metabolic Crisis is not treated, a child with MCAD can develop:
- breathing problems
- seizures
- mental retardation
- cerebral palsy
- coma, sometimes leading to death

What is the Treatment for MCAD?
The following treatments are often used for children with MCAD:
1. Do not go long times without food. Babies and young children with MCAD need to eat often to avoid low blood sugar or a Metabolic Crisis. They should not go without food for more than 4 to 6 hours. Some babies need to eat even more often. It is important that babies be fed during the night. They need to be woken to eat if they do not wake up on their own. Young children with MCAD may need to have a snack before bed and another during the night. They may need another snack first thing in the morning. Your dietitian can give you ideas for good night-time snacks. Dietitians know what are the correct foods to eat. Most teens and adults with MCAD can go without food for up to 12 hours without problems when they are well. They need to continue the other treatments for life.
2. Diet – Sometimes a low-fat, high carbohydrate diet (such as vegetables, fruits, grains) is advised. Your dietitian can create a food plan with the right type and amount of fat your child needs. Ask your doctor whether or not your child needs to have any changes in his or her diet.
3. L-carnitine – L-carnitine (Carnitech) may be prescribed for some children. This is safe and natural and helps body cells make energy. It also helps the body get rid of harmful wastes.

Things to Remember
Always call your doctor when your child has any of the following:
- poor appetite
- low energy or too much sleepiness
- vomiting
- diarrhea
- an infection
- a fever

People with MCAD need to eat extra starchy foods and drink more fluids during any illness – even if they don’t feel hungry – or they could develop low blood sugar or a Metabolic Crisis. Children who are sick often don’t want to eat. If they won’t or can’t eat, they may need to be treated in the hospital to prevent problems.
Abnormal NBS Results

- State lab notifies closest metabolic center(s)
  - Centers receive numerical data
  - In our practice, we call MDs directly only for NBS results that appear critical/urgent

- Phone consultations with providers
  - Discuss natural history and confirmatory testing
  - Discuss if referral needed now or in future
### 2013 Specimen Results*

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<thead>
<tr>
<th>Diagnosis</th>
<th>Total</th>
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<tbody>
<tr>
<td>BIOT Abnormal</td>
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<tr>
<td>GAL Abnormal 1-P Uridyl Transferase</td>
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<tr>
<td>GAL Borderline 1-P Uridyl Transferase</td>
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<tr>
<td>MSMS Abnormal</td>
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<tr>
<td>MSMS Borderline</td>
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<tr>
<td>MSMS CUD LBW</td>
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<td>MSMS General Elevation</td>
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<tr>
<td>MSMS TPN</td>
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### 2014 Jan- June Specimen Results*

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* Includes all non-normal screens (first, second, and any additional screens)
## 2013-14 Metabolic Diagnosed Cases

### Diagnosis 2013

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<td>GAL - Duarte/Galactosemia D/G</td>
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<td>MSMS - CUD - Classical</td>
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<td>MSMS - Homocystinuria - Vit B6 non-responsive</td>
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<td>MSMS - VLCAD</td>
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<td>PKU - Biopterin Deficiency</td>
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### Diagnosis January - June 2014

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<th>Male</th>
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<tr>
<td>BIOT - Biotinidase deficiency - complete</td>
<td>3</td>
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<tr>
<td>BIOT - Biotinidase deficiency - partial</td>
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<td>15</td>
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<td><strong>Total</strong></td>
<td><strong>12</strong></td>
<td><strong>7</strong></td>
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<tr>
<td>GAL - Classic Galactosemia G/G</td>
<td>1</td>
<td>2</td>
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<tr>
<td>GAL - Duarte/Galactosemia D/G</td>
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<td><strong>Total</strong></td>
<td><strong>14</strong></td>
<td><strong>10</strong></td>
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<tr>
<td>MSMS - 2MBG</td>
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<tr>
<td>MSMS - 3MCC deficiency - Infancy Onset</td>
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<td>MSMS - Citrullinemia - Classical Type I</td>
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<td>MSMS - Citrullinemia - Type II</td>
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<td>MSMS - CUD - Classical</td>
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<td>PKU - Biopterin Deficiency</td>
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<td>PKU - BPH &lt;6 mg/dL on unrestricted diet</td>
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<td><strong>47</strong></td>
<td><strong>44</strong></td>
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The Rough Numbers

- 700,000 screened/year for both NBS
- ~5000 presumptive positives (<0.7% of above)
- ~200 diagnoses (4% of above)
Positive Screens

- NBS is a screening
- Positive predictive values
  - 40% for galactosemia, PKU
  - 22% for biotinidase deficiency
  - 3% for MSUD
- Confirmatory testing needed after a screen
False Positive Screens

- This means an unaffected individual screens positive for a disorder

- Influence of feedings or TPN
  - Amino acids in TPN
  - Amino acids in specific formulas
  - MCT oil in formula
  - TPN has low or absent carnitine
False Positive NBS

- High temperatures during transport of card
  - Affects enzymes – biotinidase, GALT
- Immaturity of enzymes
  - Transient tyrosinemia
- Maternal effects
  - Low B12 or carnitine status for mother
  - Mother has a mild metabolic disorder
False Positive Screens

- Cutoff for metabolites too low
  - State lab continues to refine cutoffs
False Negative Results

- This means an affected individual is not detected by NBS
- Sampling too early or too late in life
  - Metabolite has not accumulated yet
  - Metabolite has diminished after feedings
- Individual has a disorder that is only detectable during illness
False Negative Results

- Low excretion of metabolites
  - Example, glutaric acidemia type 1
- Blood transfusion prior to obtaining NBS
- Incorrect card sampled
- Marker does not discriminate disorder well
  - Example, tyrosine for tyrosinemia type 1
- Cutoff for the metabolite is too high
False Negative Results

- Include a metabolic disorder on your differential diagnosis if the signs are present, even with normal NBS
  - Example, intermittent maple syrup urine disease
NBS: Diagnosed Disorders

- Management at metabolic center
  - Education on natural history of the condition
  - Further testing as needed
  - If needed, special diet or medications
  - Plan for sick day management
  - Genetic counseling
  - On-going care in our clinic
Case examples
Case 1

- 34 week preemie infant, DOL 5, on TPN
  - Acidosis: pH 7.12, bicarbonate 10 mM, base deficit -14
  - Ammonia 120 microM (<35 microM)
  - Lactate 4.4 mM (<2 microM)
- TPN stopped and D10 IVF started
- Metabolic consult
Diagnostic Labs

- Acylcarnitine profile, plasma or blood spot
- Urine organic acids, quantitative
- Plasma amino acids, quantitative
- Plasma carnitine
Diagnosis

- Lab markers of organic acidemias
  - Low pH, low bicarbonate, base deficit
  - +/- elevated ammonia
  - +/- elevated ketones

- Diagnosis
  - Methylmalonic acidemia (MMA)
    - Abnormal urine organic acids and acylcarnitine profile
  - DNA confirmation—MMA “mut 0” form
Treatment Strategy

- Briefly halt protein; increase calories
- Diet calculated by metabolic dietitian
- Add medications or cofactors
  - Levocarnitine
  - Test B12 response, in this case
- Avoid fasting; catabolism worsens acidosis
- Anticipate need for G-button
Metabolic Diet

- No “ready to feed” metabolic formula
- Identify the disorder and note its restricted amino acids
- Use standard infant formula to meet the restricted amino acids requirements for age
- Complete child’s prescription with metabolic formula that lacks the restricted amino acids
Metabolic Formula

- Ensure dietary goals are met—calories, fluid, energy, protein, and amino acids
- Ensure the volume prescribed is delivered
- Measure plasma amino acids after several days on new formula
- Adjust formula based on plasma amino acids, intake needs, and growth
- Repeat
Metabolic Formula

Includes both intact protein and a modified protein that is specific for the disorder.
Metabolic TPN

- Long titration of TPN with increasing feeds for this preemie
- Assistance from our pharmacists
  - TPN similar to formula—standard amino acid solution and modified amino acids for the disorder
  - Ordered from a specialty pharmacy
MMA: Outcome

- Development is usually delayed
- Poor appetite (ketosis)
- Frequent vomiting
- Complex sick day management
- Decompensation with illnesses
  - Frequent hospital stays
- Renal failure possible
Inheritance: autosomal recessive
Case 2

- 3 day old term male infant brought to ED
- Lethargic, poor feeding, floppy, low temp
- Sepsis workup and antibiotics
- Labs: normal blood gas, no acidosis, normal lactate
- Apneic spells
- Ammonia: 920 microM (normal <90)
Case 2

- If thinking about sepsis, also check NH3
  - Collect on ice, run stat, in house
  - >100 microM in a neonate gets my attention
  - In urea cycle disorders, NH3 of 200-3000+ microM can be seen
Diagnosis

- Very high ammonia and normal pH suggest a urea cycle disorder
- Confirmatory labs
  - Plasma amino acids
  - Urine organic acids
  - Urine orotic acid
  - Later - DNA testing based on above
- Ornithine transcarbamylase (OTC) deficiency, in this case
X-linked inheritance
Emergent Treatment

- Halt protein briefly and increase calories
- Lower ammonia as quickly as possible
  - Hemodialysis or ECMO
  - NH3-scavenging meds by IV
- Resume protein intake with essential amino acids by NGT
Long-Term Treatment

- Oral NH3-scavenging meds and amino acids to replenish urea cycle
- Dietary management
- Avoid fasting/catabolism
- Anticipate need for G-button
UCDs: Outcome

- Development is poor if child had elevated ammonia for extended period
  - By the time of presentation, brain is injured
- Complex sick day management
- Frequent hospitalization with illness and hyperammonemia
- Liver transplant an option
Case 3

- Called by PCP about a child with an abnormal NBS report, now 9 days old
  - Leucine 593 microM (<500)
  - Valine 417 microM (<476)
- Advised on f/u labs and signs of illness for MD and family to monitor
- Hospitalized locally next day and then transferred to our NICU
History

- Parents’ history
  - He “smelled like pancakes” on DOL 6
  - Slowly lost ability to feed by breast, switched to bottle, decreased interest in feeding
  - Moving arms and legs in “funny” way
  - More irritable and then less responsive
Diagnosis

- Plasma amino acids
  - Leucine 2496 microM (47-160)
  - Isoleucine 139 microM (26-91)
  - Valine 122 microM (64-336)
  - Alloisoleucine (present = MSUD)

- Urine organic acids were diagnostic

- The child does smell of maple syrup when his leucine levels are >500 microM
Diagnosis

- Maple syrup urine disease (MSUD)
  - May not be recognized until NBS returns
  - Child may or may not have maple odor in sweat and urine (be aware of fenugreek)
  - Abnormal posturing and irritability
  - +/- elevated ketones
Fenugreek
Treatment

- **MSUD**
  - Briefly halt protein; increase nonprotein calories
    - May add insulin to allow increase in GIR
  - Dialysis to lower leucine (10-20x normal)
  - Metabolic formula
    - Careful balance of the 3 amino acids
  - Thiamine as a vitamin cofactor
  - Avoid fasting; anticipate G-button
Inheritance: autosomal recessive
Outcome

- Development may be delayed
  - More variable than the outcomes in organic acidemias and urea cycle disorders
- Complex sick day management
- Hospitalization with illness or poor feeding; leucine intoxication
  - Frequent hospital stays
NBS: Final Points

- NBS is a screening process that requires confirmatory testing
- TX NBS program tests for the 29 core disorders and 24 secondary disorders recommended by ACMG
- ACT and FACT sheets are available for providers and parents
Final Points

- Metabolic centers are available to direct initial testing and management
- TX NBS lab continues to refine techniques to decrease false positives and false negatives
- Neonatal disorders may present before the NBS has returned
Final Points

- We have seen many, many successful outcomes in individuals detected by NBS