SHORT AND LONG OF NEWBORN SCREENING

The New England Experience in Follow-Up for Out-of-Range Markers for Glutaric Aciduria-II

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New England Newborn Screening Program

2013 Newborn Screening and Genetic Testing Symposium
Glutaric Aciduria- Type II

- Multiple Acyl-CoA Dehydrogenase Deficiency (MADD)
- Electron transfer flavoprotein enzymes (ETFA, ETFB, or ETFDH).
- Long, Medium & Short-Chain Acyl-CoA, Isovaleryl CoA and Glutaryl CoA dehydrogenases
Clinical Presentation: GA-II

Severe / Neonatal
- Congenital Anomalies
- Hypotonia
- Hepatomegaly
- Sweaty Feet Odor
- Metabolic Acidosis
- Hypoglycemia
- Liver Dysfunction
- Death

Mild / Late
- Myopathy
- Exercise Induced Muscle Pain
- Metabolic Crises

Individuals with disorder are most susceptible during periods of increased metabolic requirements (illness) and decreased glucose intake (fasting, vomiting)
Elevation of Multiple Acylcarnitines

- Plasma Acylcarnitines
- Urinary Organic Acids
- Urinary Acylglycines

Routine Laboratory Investigations

PAC: GA-II Profile
UOA/UAG: GA-II Profile

Case Confirmed

Gene Analysis/Enzyme Assay Optional

Normal

Enzymatic Assay
- GA-II Profile
- Mutation/s Identified

Gene Analysis
- No Mutations Identified
- Normal Enzymatic Assay

False Positive
Elevation of Multiple Acylcarnitines (> 2)
- C4
- C5
- C8
- C5DC
- C12, C14, C14:1

Profile not consistent with another Fatty Acid Oxidation Defect.
- MCAD: C8 & C5DC
- VLCAD: C12, C14, C14:1 (C14:1 >C14)
Neonates with Elevations of Multiple Acylcarnitines
(in screening specimens collected within 30 days of life)

February 1999-Dec 2012 (MA, ME, NH, RI, VT)
1.5 Million Neonates

Wt > 1.5 Kg
- 82
  - 21 Initial Specimen
  - 1 Repeat Specimen

Wt ≤ 1.5 Kg
- 61 Initial Specimen
  - 11 Repeat Specimen
  - 50 Repeat Specimen
Very Low Birth Weight (< 1.5 Kgs) Neonates with Elevations of Multiple Acylcarnitines

Initial Specimen
- 61
- 11
  - 5
    - 0 Deceased
    - 0 Deceased
  - 3
    - 2 Deceased
    - 3 Deceased
  - 3
    - 0 Deceased
    - 0 Deceased

Not Initial Specimen
- 50
- 25
  - 2 Deceased
  - 4 Deceased
  - 4 Deceased
- 18
  - 0 Deceased
  - 4 Deceased
  - 4 Deceased
- 7
  - 0 Deceased
  - 4 Deceased
  - 4 Deceased

Follow-up Specimen
- 61
- 11
- 5
- 3
- 3

Biomarker Profile
- C4 (10) C5(9), C5DC(4), C8(2)
- Also seen C0 (3)

Follow-up Specimen
- 50
- 25
- 18
- 7

Biomarker Profile
- C5(49), C8(44), C5DC (23), C4 (22)
- Also seen C0 (29), Leu (7)
- No C14

10 on TPN/HA with Lipids
Specific Work-up for GA-II not Done

1 case of GA-II ( CC4, C5, 14 elevated; C8 normal)
No follow-up specimen
Neonates (> 1.5 Kgs) with Elevations of Multiple Acylcarnitines

(in screening specimens collected within 30 days of life)

Initial Specimen

21

20

9

0 Deceased

1 : GA-II
1 : GA-II Carrier
3: Incomplete W/U

4

0 Deceased

2 : GA-II
1: MCAD&VLCAD Carrier
1: Clinically well; Incomplete W/U

7

5 Deceased

3 : GA-II
1 : GA-II Carrier
1: Incomplete W/U

Not Initial Specimen

1

Follow-up Specimen

Follow-up Specimen

Deceased

1

On TPN/HA with Lipids Mitochondrial Disorder

0 Deceased

1 : GA-II
1 : GA-II Carrier
3: Incomplete W/U

1 : MCAD&VLCAD Carrier
1: Clinically well; Incomplete W/U

Incomplete W/U
### Multiple Acylcarnitine Profiles (Neonates > 1.5 Kgs; Initial Specimen OOR)

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<th>C3</th>
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<th>C5</th>
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**UMASS MEDICAL SCHOOL | COMMONWEALTH MEDICINE**

**NEW ENGLAND NEWBORN SCREENING PROGRAM**
(Neonates > 1.5 Kgs; Initial Specimen OOR)

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<th>Outcome</th>
<th>Repeat Screen</th>
<th>([C4xC5xC8xC14]/[C0xC3])</th>
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Glutaric Aciduria- II Confirmed Cases
4/7 Deceased

• Prenatal Findings:
  IUGR, Oligohydramnios (1/4)

• Congenital Anomalies (3/4)
  Renal cysts (2/3), Cystic lesions in brain (1/3)
  Cleft palate (1/3)

• Initial Clinical Presentation (Birth-DOL 2)
  Hypotonia (3/4), Respiratory Distress at Birth (1/4)
  Change in Mental Status / Seizures (2/4)
  Cardiac Arrest (1/4)
Glutaric Aciduria- II Confirmed Cases

- **Laboratory Findings:**
  - Hypoglycemia, Acidosis (4/4)
  - Hyperammononemia (1/4)

- **Diagnostic Testing:**
  - GA-II Profile on UOA, PAG and PAC (4/4)
  - Enzymatic assay (Performed on 1)
  - DNA Studies (Performed on 1)

- **Deceased:** On DOL 3 (3/4), DOL 7 (1/4)
Case 5

- Clinically Asymptomatic
- NBS DOL 2: Screen positive for GA-II
- Repeat Screen DOL 7: Markers in range.
- Diagnostic testing (In 1st month):
  - UOA: EMA only
  - UAG: Hexanoyl & Butryl.
  - Enzymatic activity: Mild increase in C4 (SCAD)

? SCAD
Case 5: Clinical Course

• 7 months (GI Illness)
  Lost babbling, Hypotonia, Hypoglycemia

• 1 year: Food aversion
  Hypoglycemic Episodes, G-Tube

• 1-1/2 Year (During Illness)
  Biochemical studies c/w GA-II
  DNA & Repeat Enzymatic Studies: GA-II

• Current (Age 11 years):
  Height & Weight 50th%ile; Cognitively intact
  G-Tube feeding at night, Mild hypotonia,
  Difficulty with sustained activities
Case 6

- **DOL 2**: Pale, Tachypnea. Anemia (h/o intrauterine bleed), Mild hypoglycemia that resolved with IV dextrose.
- **NBS DOL 2**: Screen positive for GA-II (as was repeat screen)
- **Diagnostic Testing**: GA-II Confirmed
- **Current (Age 5 years)**
  - Mild hypotonia. Cognitively intact.
  - G-Tube feeding at night
  - Metabolic decompensations when ill.
  - Persistent elevations of LFT’s
Case 7

- NBS DOL 3: Screen positive for GA-II
- Evaluated in ER: Asymptomatic, but glucose 30 mg/dl. LFT’s slightly high.
- Diagnostic Testing:
  - Urine: C/W GA-II, PAC: ? VLCAD
  - DNA: 1110C>G / 250G>A in ETFDH gene
  - Enzyme Test: Pending
Conclusions

• Severe form not likely to benefit from Screening
• Mild forms may have normal repeat screens or atypical biochemical profiles
• Enzymatic/Molecular studies should be completed; even if initial biochemical tests are normal, especially in neonates with a positive screen on initial specimen when not on TPN/lipids.
• C14 (& other long chain acylcarnitine species) are typically not seen as part of multiple acylcarnitine elevations due to TPN/lipids.
Contributors

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