

# Short-term outcomes in medium-chain acyl-CoA dehydrogenase (MCAD) deficiency: Use of a long-term follow-up database Inborn Errors of Metabolism-Information System



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## Abstract

- To improve outcomes from newborn blood spot screening (NBS), metabolic clinicians in states participating in the HRSA-funded Region 4 Genetics Collaborative (IL, IN, KY, MI, MN, OH, WI) agreed that they would collaborate in gathering data about children after NBS. Our initial goals from this activity were twofold: we wanted to show that metabolic practitioners could efficiently gather information about patient outcomes in a systematic fashion and we wanted longitudinal information about clinical outcomes after NBS. We initiated data collection in January 2007 with a focus on MCAD deficiency. We wanted to test the hypotheses that children with the highest C8 screening values would be most symptomatic with a secondary question regarding the nature of mutations found in these children with the hypothesis that the highest C8 values would be found in children who are 985 A>G homozygotes.
- Results: As of May 2009, 42 infants ascertained by NBS (with C8 as the informative value) had entries with information about lab abnormalities or other symptoms at the time of initial metabolic presentation. Of the 21 patients with the lowest C8 values (range 0.4-8.69, "lo") 17 had 2 mutations ascertained; 5 were 985 A>G homozygotes. Of the 21 patients with the highest C8 values (range 8.97-38.8, "hi") 16 had two mutations ascertained; 11 were 985 A>G homozygotes. Of the 21 lo range patients, one was noted to have abnormal liver function tests, one had respiratory distress due to prematurity, one was admitted for possible apnea but apnea was not confirmed. All others had no labs done, no abnormal labs and/or had no symptoms. Of the 21 hi range patients, six had either a lab abnormality or symptom (lab findings: (lab values suggesting) dehydration, hypoglycemia, elevated liver function tests; symptoms: loose stools, fever, pallor, limp, poor breast-feeding.) Of these, three had both a lab abnormality and symptom.
- We conclude that a long-term follow-up database can be successful in ascertaining systematic data about short-term follow-up for children with inborn errors of metabolism. Further, though preliminary, higher C8 values on NBS for MCAD deficiency are associated with a higher risk of being 985 A>G homozygote and having a symptom or lab abnormality at the time of NBS.
- Supported by HRSA MCHB U22MC03963 – Priority 2 Project: Follow-up Activity

## Region 4 Collaborators: our Priority 2 Project Workgroup

Metabolic Clinicians and State Health Department NBS Specialists

- Illinois
- Indiana
- Kentucky
- Michigan
- Minnesota
- Ohio
- Wisconsin



- Heartland Centers (Missouri, Oklahoma, othersxx [confirm all])

## Use a condition registry as a research platform

- Document interventions that can be assessed with data in IBEM-IS
- Plan initial projects that examine
  - “Natural” history
  - Short term outcomes

*At initial enrollment we request registry subjects to consider consent to allow continuing contact, anticipating engaging them as participants in future research trials.*

## MCAD deficiency: useful model condition for IBEM-IS

- Sufficiently rare that no one practitioner sees enough
- Sufficiently common that cooperation in data gathering can yield relatively rapid meaningful data
- Some, but not complete agreement about treatment strategies

## Hypotheses developed to assess initial data collection on MCAD deficiency patients

- Children with the highest C8 screening values will be most symptomatic
- The highest C8 values will be found in children who are 985 A>G homozygotes

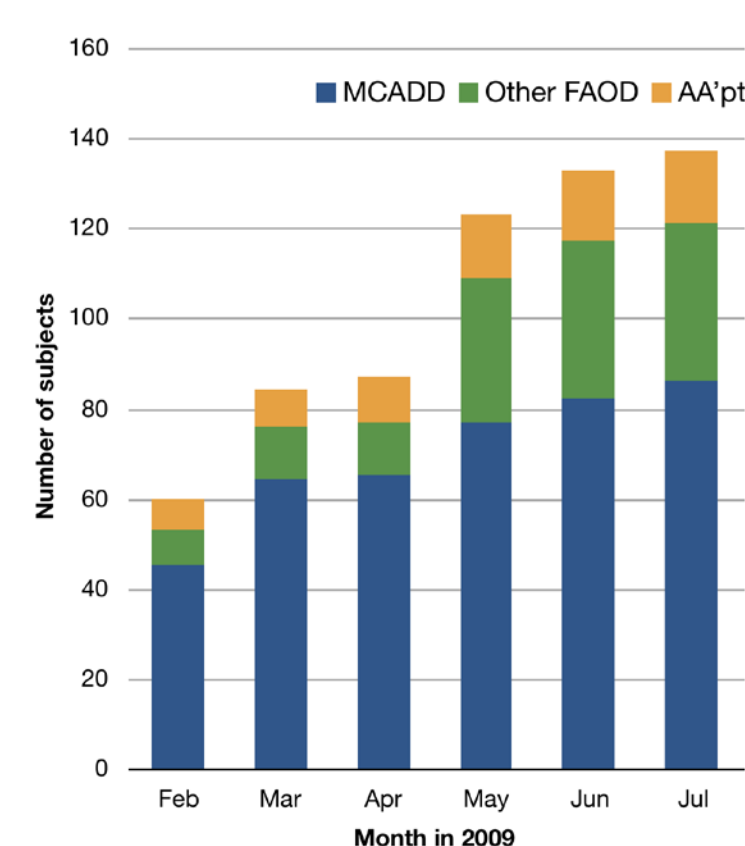
## Methods for collecting project data using the IBEM-IS

- Obtain prospective informed consent
- Ascertain data as clinic visits begin
- Gather data elements for initial presentation “enrollment” and at each visit “interval”
- Enter data at each clinic visit via web-based entry forms.

**Web-based data entry**

**Can generate paper forms for data collection in clinic**

## R4 cumulative enrollment Feb-Jul 2009: Analysis from all enrollments



- 42 infants ascertained by NBS (C8 as informative value)
  - Report from system sought data about lab abnormalities or other symptoms at the time of initial metabolic presentation.
  - (many had genotype done; data sought in report)
- Stratified by C8 values
  - Bottom half “lo” range 0.4-8.69 uMo/mL
  - Top half “hi” range 8.97-38.8 uMo/mL

## Higher C8 values on NBS are associated with more symptoms/laboratory findings

- “lo” range patients: 18 had no labs done, no abnormal labs and/or had no symptoms
  - 1 - abnormal liver function tests; dehydration
  - 1 - respiratory distress due to prematurity
  - 1 - admitted for possible apnea but apnea was not confirmed, poor feeding.
- “hi” range patients: 14 had no labs done, no abnormal labs and/or had no symptoms
  - 1 – loose stools
  - 1 – dehydration and irritability
  - 1 – fever, irritability and hypoglycemia
  - 1 – pallor, limp, poor feeding, hypoglycemia
  - 1 – poor breast feeding, lethargy, hypoglycemia, uric acid elevated
  - 1 - hypoglycemia
  - 1 - Jaundice

## Infants with “hi” C8 value on NBS are more likely to be 985 A>G homozygotes

- Lo range infants
  - 17 with two mutations
  - 5 were 985 A>G homozygotes
- Hi range infants
  - 16 with two mutations
  - 11 were 985 A>G homozygotes

## Conclusions

- Higher C8 values on NBS are associated with an increased risk for symptoms for affected newborns
- Infants with higher C8 values are more likely to be 985 A>G homozygotes
- IBEM-IS provided a successful platform for investigating hypotheses
- Collaboration in data gathering may help us improve outcomes after newborn screening*

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