2017 Alabama Newborn Screening Conference

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Inherited Disorders of Metabolism

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Inherited Disorders of Metabolism Definition

- Clinical or biochemical condition caused by an enzyme deficiency
- Enzyme may have completely or partially absent activity: so patient can present early or later
- Enzyme is deficient as a result of genetic mutation

Inherited Disorders of Metabolism Biochemistry

- Biochemical abnormality precedes signs and symptoms: a latent period where the biochemistry is abnormal but the infant is well
- This latent period is basis of newborn screening
- Want to diagnose baby before illness is apparent!

Inherited Disorders of Metabolism Biochemistry

- The abnormality is not always an enzyme
- However, the abnormality does always involve a biochemical pathway
- So there should be some biochemical test available for the disorder
- We do screen for the full recommended panel

NORMAL	IEM
A→B	A↛B
↓	↓
C	C

so: ↑ A (substrate)
↓ B (product)
↑ C (minor product)

Alabama Newborn Screening for Inherited Disorders of Metabolism

- Most common abnormalities
  - Premature infants
    - Many false positives due to TPN
    - "expected abnormalities in light of clinical setting"

Alabama Newborn Screening for Inherited Disorders of Metabolism

  - High tyrosine level due to enzyme immaturity or liver disease
- 4 most common diagnoses of confirmed metabolic disorders

Alabama Newborn Screening for Inherited Disorders of Metabolism

  - hyperphenylalaninemia
  - MCAD
  - VLCAD
  - galactosemia

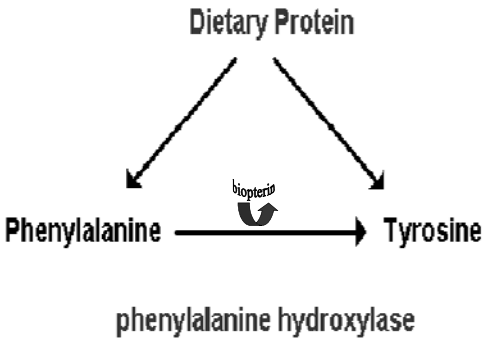
2011 Diagnoses	2016 Diagnoses
Hyperphe=4	Hyperphe=4
PKU=5	PKU=2
Galactosemia=0	Galactosemia=4
Duarte Galactosemia=10	Duarte Galactosemia=4
VLCADD=1	VLCADD=3
VLCADD Carriers=4	VLCADD Carriers=3
MCADD=5	MCADD=3
MCADD Carriers=12	MCADD Carriers=0
CUD=2	CUD=1
CUD Carriers=0	CUD Carriers=2
Maternal 3MCC=1	Maternal 3MCC=0
Citrullinemia Carrier=0	Citrullinemia Carrier=2
GA1=1	GA1=0

PKU

PKU History

- 1934: Fölling first described unusual compound in urine of 2 intellectually disabled siblings
  - Really the story of a determined mom and a doctor who listened!
- 1951: successful treatment with diet
- 1960: Guthrie test developed and newborn screening started

The discovery of phenylketonuria: the story of a young couple, two retarded children, and a scientist.
Centerwall SA, Centerwall WR.
Pediatrics. 2000 Jan;105(1 Pt 1):89-103.



NORMAL

A→B

↓

C

IEM

A-x→B

↓

C

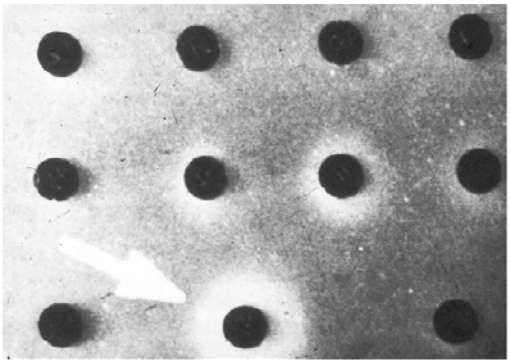
PKU: Clinical Untreated

- **Gradual onset (first year of life) of significant intellectual disability**
  - **50-70% IQ < 35**
  - **90% IQ < 65**
  - **2-5% IQ normal**

PKU: Clinical Untreated

- **Fair pigmentation for ethnic group**
- **Eczema**
- **Musty odor**

PHENYLKETONUIA



PKU Treated

- Normal IQ!!
- Best outcome with strict, lifelong adherence to diet
- Discontinuation of diet will result in loss of IQ points and psychological abnormalities for most patients
- Diet treatment in first few weeks of life leads to normal outcome

INITIAL WORK UP FOR PKU

- Differential diagnosis of elevated phenylalanine levels
  - PKU
  - Biopterin defects
  - Infant on TPN

INITIAL WORK UP FOR PKU

- Obtain plasma amino acids and urine and blood for biopterin studies before come to clinic
- In general, we do not obtain any genetic testing

Initial clinic visit: PKU

- Confirm diagnosis
  - Initiate treatment as soon as family notified
  - Clinic visit ASAP
    - Confirm diagnosis same day as clinic visit
  - In most patients, treatment initiated within 7-14 DOL

Initial clinic visit: PKU

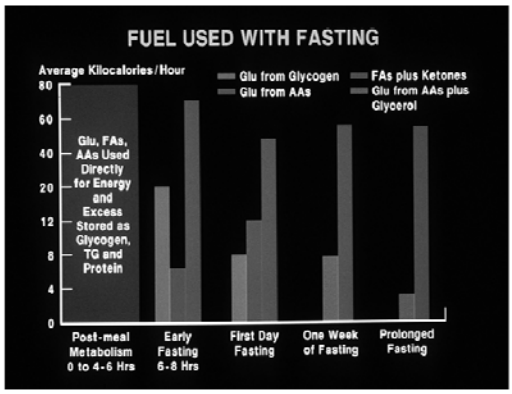
- Education about
  - Newborn screening
  - Condition
  - Genetics

Initial clinic visit: PKU

- Diet explanation
  - Washout
  - Daily diet: changes weekly based on levels
- Lots of phone numbers and contact info and f/u visit within 7-10 days

INBORN ERRORS OF FATTY ACID METABOLISM

We screen for several, but just discuss our more common today

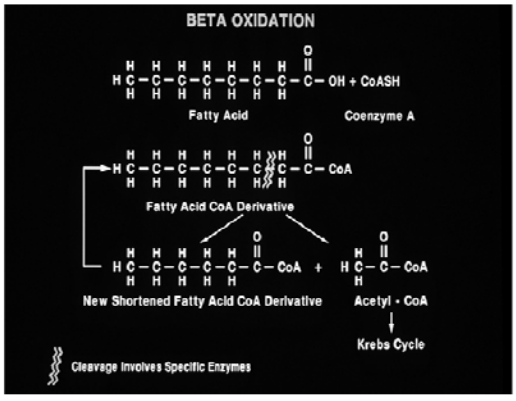


COMMON FEATURES OF FATTY ACID OXIDATION DEFECTS

- <u>Metabolic decompensation during fasting</u>
  a) In children: fasting, especially with illness decreased oral intake, increased energy needs
  b) Altered mental status progressing to coma
  c) SIDS (1-3%)
  d) Positive family history, recurrent episodes

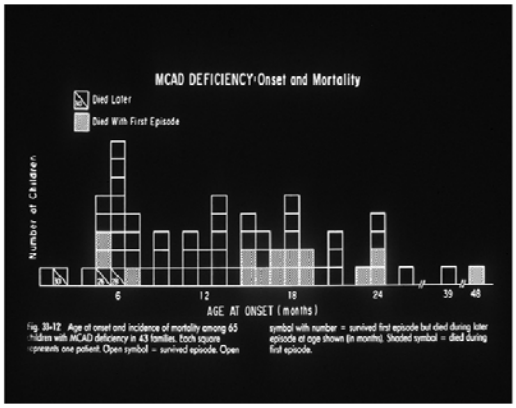
COMMON FEATURES OF FATTY ACID OXIDATION DEFECTS

- Metabolic decompensation: other precipitants:
  a) Exposure to cold
  b) Excessive alcohol ingestion
  c) Exercise
  d) Fat rich diet
  e) Prolonged fasting



MCAD Untreated

- Patients are clinically well
- They develop a "routine" childhood illness with loss of appetite and usually with vomiting
- They may have an episode with longer recovery than other family members OR
- They may be found dead 1-3 days into course of illness



Disorders of FAO β 0xidation CLINICAL PRESENTATIONS Medium Chain Fats

- For unscreened (undiagnosed) patients:
  - Death in 25-30% of patients with first episode
  - Neurocognitive residual in 32% survivors of an episode of metabolic decompensation

Disorders of FAO β 0xidation CLINICAL PRESENTATIONS Medium Chain Fats

- NBS changes all of this
  - 5 fold higher risk of death in unscreened patients

Initial Clinic Visit: MCAD

- Send testing to confirm diagnosis
  - Initiate treatment with first phone call, prior to confirmation
  - Clinic visit ASAP

Initial Clinic Visit: MCAD

- Education about
  - Newborn screening
  - Condition
  - Genetics

Initial Clinic Visit: MCAD

- Plan for intercurrent illnesses
  - mild illnesses with normal appetite
  - Illnesses which meet our admit criteria
- Lots of phone numbers and contact info and f/u visit within 7-10 days

Disorders of FAO β Oxidation TREATMENT

- GOAL:
  - Avoid fasting, especially fasting with increased metabolic rate
  - Provide appropriate types of fat in diet

Disorders of FAO β Oxidation TREATMENT

- METHODS:
  - Normal meal/snack pattern
  - cornstarch
  - Increase calories from sugar when needed
  - Carnitine in some
  - Treat illness aggressively

Disorders of FAO β 0xidation CLINICAL PRESENTATIONS Medium Chain Fats

- Known diagnosis:
- Admit for illness criteria
  - vomiting ≥2 times in < 8hours
  - Fever of 101º for > 4 hours
  - Diarrheal illness

Disorders of FAO β 0xidation CLINICAL PRESENTATIONS Medium Chain Fats

  - Anything we think needs admitting!
- If they look very ill, or glucose is low
  - → we have waited too long!

MCAD: Metabolic Decompensation

What exactly are we doing?

IV glucose: shutting down ongoing fat metabolism, decreasing substrate into system

Carnitine: promoting metabolic flux

AVOIDING FURTHER DEAD CHILDREN

Current problems with evaluation for MCAD

- Alert values only
  - This means we work up any newborn who meets our criteria
- Often: quite clear have MCAD
- Sometimes: values are not as clear cut
  - Ancillary testing helps with this
- UNABLE TO GET MOLECULAR ANALYSIS ON MEDICAID PATIENTS

Disorders of FAO β 0xidation CLINICAL PRESENTATIONS

Long chain fats: 3 Clinical Presentations

- Early onset and severe (occasionally in utero)
  - Heart, liver, hypoketotic hypoglycemia
  - Significant fatality rate

Disorders of FAO β 0xidation CLINICAL PRESENTATIONS

Long chain fats: 3 Clinical Presentations

- Infancy onset, milder
  - Onset with infections
  - Heart, liver hypoketotic hypoglycemia

Disorders of FAO β 0xidation CLINICAL PRESENTATIONS

Long chain fats: 3 Clinical Presentations

- Later onset and myopathic
  - Often induced by exercise or infection
  - Muscle: may include rhabdomyolysis
  - Early onset presentations who survive may evolve to this

VLCAD

- If 3 different presentations, how do we decide what the baby is at risk for?
  - Ancillary biochemical testing not helpful (may normalize)
  - Can do skin fibroblasts
    - Mildly invasive procedure
    - Takes weeks for results

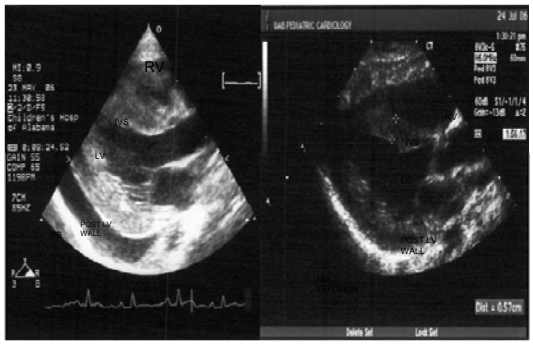
VLCAD

- Molecular
  - Expected clinical presentation based on mutations
- Cannot get molecular testing on Medicaid patients
  - We can order but Medicaid won't pay and family will get large bill

VLCAD

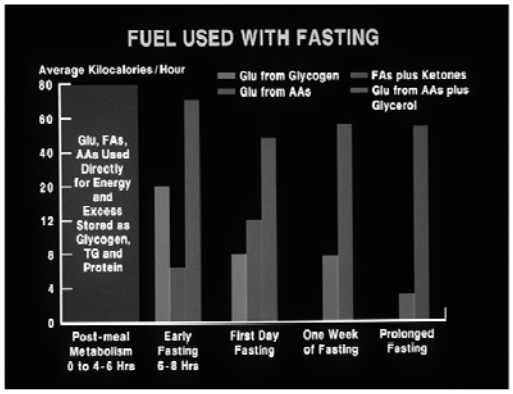
- Insurance maybe 80/20
  - Family may get large bill
- This really hurts our ability to care for these patients

VLCAD: echo pre and post RX



GALACTOSEMIA

Inborn Error of Carbohydrate Metabolism



Inherited Disorders of Carbohydrate Metabolism

1. Deficiencies in stored glucose (glycogen) metabolism
2. Deficiencies in ability to metabolize ingested sugars (galactose, fructose)
3. Deficiencies in muscle carbohydrate metabolism: metabolic myopathies
4. Many things (hormones) affect carbohydrate metabolism

GALACTOSEMIA

- EARLY CLINICAL
  - FTT
  - vomiting and diarrhea
  - LIVER: hepatopathy: direct bili, coags, transaminases

GALACTOSEMIA

- LABORATORY
  - elevated LFT's/coagulopathy
  - E Coli infection
  - positive urine reducing substances: not glucose

GALACTOSEMIA

- LATE CLINICAL
  - ovarian failure
  - speech delay

GALACTOSEMIA NOW

- Most patients detected by newborn screening before becoming ill
- Carriers are detected by newborn screening
- Approximately 1 new case of classic galactosemia/year
- Many carriers diagnosed/year
- Must be on galactose to be symptomatic

How do we diagnose?

- State lab measures enzymes but
  - This is just a screen
  - Get result of < 2.5 u/dl, presumed positive
  - Often picks up carrier

How do we diagnose?

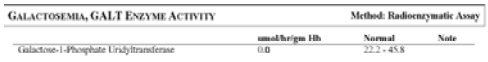
- So how do we figure out who has disease?
- Galactosemia genes can come in 1 of 3 ways
  - Normal "N": normal enzyme activity
  - Classic galactosemia "G": no enzyme activity
  - Duarte "D": some residual enzyme activity

How do we diagnose?

- We often pick up, as positive, babies who have
  - NG: no treatment required
  - DG: treatment probably not required but we do change formula And ongoing studies about treatment requirements

How do we diagnose?

- We would like to do genetic confirmation
  - that will tell us exactly what infant has
- Currently, we base our specific diagnosis on enzyme activity
- Usually effective, can be a little iffy



GALACTOSEMIA, GALT ENZYME ACTIVITY			Method: Radioenzymatic Assay
	umol/hr/gm Hb	Normal	Note
Galactose-1-Phosphate Uridyltransferase	0.0	22.2 - 45.8	

How do we diagnose?

- Cannot get molecular testing on Medicaid patients
  - We can order but Medicaid won't pay and family will get large bill
- Insurance maybe 80/20
  - Family may get large bill
- This really hurts our ability to care for these patients

The world of lab testing coverage must keep pace with what is necessary, and least expensive, in 2017

Practicing 20th century medicine in 21st century

PKU & MCAD Examples of Why NBS Works

- PKU:
  - Patients develop severe brain damage over time
  - Early treatment prevents the brain damage
  - We can detect it early enough to prevent any brain injury from occurring

PKU & MCAD Examples of Why NBS Works

- MCAD:
  - Patients are well and normal until their first significant illness
  - ⅓ to ½ of patients with undiagnosed MCAD will die with their first significant illness
  - These deaths are prevented by knowing that the child has MCAD and treating with IV glucose for illnesses

PKU & MCAD Why difference in Initiating Treatment?

- PKU:
  - Treatment is restriction of phenylalanine by restricting protein and adding special metabolic formula
  - This can be quite dangerous to do if you do NOT have PKU or hyperphenylalaninemia

PKU & MCAD Why difference in Initiating Treatment?

- MCAD:
  - Treatment is primarily IV glucose with significant intercurrent illness
  - So not dangerous to treat with IV glucose if you do NOT have MCAD
  - very dangerous to NOT treat with IV glucose if you do have MCAD and develop an illness

Current Problems in Metabolic Newborn Screening

- Too many repeats!!
  - Do enough and something will show up as abnormal
  - Just do the gold standard test
  - Especially true in NICU patients
  - Follow protocol but beyond that…

Current Problems in Metabolic Newborn Screening

- Sending incorrect confirmatory testing
  - ASK ALICIA 205-996-6983

Current problems in Metabolic Newborn Screening

- Inability to get genetic analysis
  - Not just for the ones I discussed but true for many of these
- Still often called "the PKU test"
- DO NOT CALL IT THE PKU TEST!!

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