Inborn Errors of Metabolism

- The body is a factory....

- Inborn errors of metabolism are rare genetic disorders in which the body cannot properly turn food into energy. The disorders are usually caused by defects in specific proteins (enzymes) that help break down (metabolize) parts of food. (Medline Definition)

Metabolic Pathway

Digestion and Fasting

How is Expanded Newborn Screening Different?

- Tandem Mass Spectrometry (MS/MS)
  - Uses electrical and magnetic fields to separate and measure the mass of the charged particles

MS/MS

- Over 20 metabolic conditions screened
  - Amino acidemias
  - Organic acidemias
  - Fatty acid oxidation disorders
  - Urea Cycle Disorders
  - Combined frequency of 1 in 4,000
- MS/MS does not replace traditional NBS!
  - Most disorders on traditional panel cannot be screened for by MS/MS
Aminoacidopathies
Enzyme deficiency in the breakdown of amino acids
- Most patients present after the first month of life
PKU
- Build up of phenylalanine “phe”
- Toxic to the brain
- Without treatment, can lead to MR, seizures, and spasticity
Tyrosinemia
- Build up of tyrosine
- Toxic to the liver
- Without treatment, can result in liver failure
Homocystinuria
- Build up of homocystine is toxic
- Brain = seizures and MR
- Eyes = lens dislocation
- Bones = marfanoid habitus
- Coagulation = strokes, pulmonary embolism
- Differential DX = Marfan syndrome/connective tissue disorders

Urea Cycle disorders
- Subcategory of aminoacidopathies
- Urea cycle is used to excrete nitrogen waste (urea) byproduct of protein metabolism
- Ammonia detoxification
- Block in pathway results in increased ammonia levels

Urea Cycle Disorders
- Presentation
  - Any age
  - Common in infancy
  - Initially healthy baby first few days of life
  - Progressing to symptoms of poor feeding, vomiting, lethargy, irritability, and hyperventilation
  - Quickly can progress to apnea, coma and death
  - Labs look normal!
  - Very high ammonia levels!!!
- Organic Acidemias
  - Enzyme deficiency in intermediary metabolism of amino acids results in characteristic accumulations of metabolites in urine
  - Presentation
    - Any age
    - Severe neonatal onset form
      - Initially health progressing to poor feeding, vomiting, and lethargy
      - Acidosis and ketonuria
      - Hyperammonemia
    - Bone marrow suppression
    - Chronic intermittent late-onset form (>1 year)
      - Present during illness or fasting
    - Chronic progressive form
      - Sometimes asymptomatic
- Organic Acid Disorders
  - Methylmalonic Acidemias (MMA)
  - Propionic Acidemia (PA)
  - Glutaric Acidemia – type 1 (GA 1)
  - 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency (HMG)
  - 3-Methylcrotonyl-CoA Carboxylase Deficiency (3MC)
  - 3-Methylglutaconyl-CoA Hydratase Deficiency (MGA)
  - Isovaleric Acidemia (IVA)
  - Multiple-CoA Carboxylase Deficiency
  - Beta-ketothiolase deficiency
- Fatty Acid Oxidation Disorders
  - Enzyme deficiency in fatty acid oxidation
  - Fatty acids used most often during fasting and illness
  - Used in liver, heart, and muscle
    - Liver – no ketones can be made = nonketotic hypoglycemia
    - Heart – cardiomyopathy and arrhythmia
    - Muscle – rhabdomyolysis and myoglobinuria
  - Varying fat chain length
    - Longer the chain, the more severe the disorder
    - Short chain acyl-CoA dehydrogenase def = benign
    - Medium chain acyl-CoA dehydrogenase def = moderate
Fatty Acid Oxidation Disorders

- Severe types
  - Symptoms during first few days of life
  - Nonketotic hypoglycemia = poor feeding, lethargy, etc.
  - Cardiomyopathy and arrhythmia
  - In rare cases, multiple congenital anomalies
- Milder types
  - Symptoms only when triggered by illness, fasting, and extreme exercise
  - Nonketotic hypoglycemia = poor feeding and lethargy during illness or fasting

Common inheritance pattern

MCAD Deficiency: Beta Oxidation

- Long chain fatty acids
- Medium chain fatty acids
- Short chain fatty acids
- Ketones

MCAD Deficiency: Clinical Findings

- Presentation triggered by illness which can lead to prolonged fasting
  - Lethargy
  - Vomiting
  - Coma
  - Cardiopulmonary arrest
  - Muscle weakness
  - Hepatomegaly
  - Sudden unexplained death
    - 1 in 100 cases of SIDS due to MCADD
  - Age of presentation is highly variable
    - High risk of sudden death in unrecognized patients
    - 20-25% of patients with MCADD die with their first episode of illness

Case Example # 1

- Asymptomatic female with an initial positive NBS
- Normal clinical status
- Acylcarnitine profile fits pattern for MCAD deficiency
- No other abnormal analytes
- Diagnostic tests recommended
  - Acylcarnitine profile (ACP)
  - Urine Organic Acids (UDA)
  - Urine Acylglycine
- Interim recommendations to avoid fasting and vigilance of illness
  - Second newborn screen ordered instead
  - Came back normal
  - Is this truly MCAD Deficiency? What next?
Case Example #1

- With FAOD, first newborn screen is more telling than the second
- Unlike aminoacidopathies
- Often times, the second newborn screen is normal
- Diagnostic tests recommended after initial first screen
- Continued to recommend diagnostic tests and provide recommendations while awaiting results
- Diagnostic tests:
  - Acylcarnitine profile = positive for MCADD
  - Urine Acylglycine = positive for MCADD
  - Free/total carnitine = normal
  - Not uncommon

Glutaric Acidemia Type 1: Clinical Findings

- Macrocephaly (~75%)
- Baseline MRI/CT
  - Frontotemporal Atrophy
  - ~80% of presymptomatic patients will have frontotemporal atrophy
  - Delayed myelination
  - Chronic subdural effusions
  - Hematomas
- Differential Diagnosis
  - Child Abuse: Prone to suffer acute subdural hemorrhages and retinal hemorrhages after minor head trauma
  - Around 1 yr of age when child is beginning to walk

Glutaric Acidemia Type 1: Presentation

- Normal development until initial neurological crisis
- Soft neurological signs at birth
- Irritability/instability
- Truncal hypotonia
- Feeding difficulties
- Developmental delay due to acute encephalopathic episode
  - Preceded by infection
  - Loss of head control, sucking/swallowing reflexes, sitting, pull to stand
- Neurological Signs due to irreversible striatal damage
  - Dystonia
  - Choreoathetosis
  - Normal cognition

Glutaric Acidemia Type 1: Prognosis

- Highly variable condition
- Interfamilial variability
- Early diagnosis can ensure treatment is started early to help prevent neurological sequelae
- Treatment helps the majority of kids
  - 10-30% of patient may not completely benefit from treatment
  - Neurological damage is irreversible and treatment is ineffective
  - After encephalopathic crisis
    - 75% do not recover
    - 40% died early
    - 5% did recover completely
  - Anticipatory guidance is difficult to provide!
Case #2

- Asymptomatic female with an initial positive NBS
  - Elevated acylcarnitine strongly suggestive of Glutaric Acidemia Type 1 (GA1)
  - CSDC (glutarylcarnitine)
  - No other abnormal analytes
- Clinical status normal
  - Normal OFC
- Interim Recommendations
  - Avoid fasting
  - Vigilant of illness
  - Family awareness

3MCC deficiency

3MCC symptoms

- Infants normal at birth.
- Symptoms often occur after 3 mo of age but may not appear until adulthood or never.
- Symptoms related to metabolic crises triggered by infection, illness, prolonged fast, large protein intake.
- Symptoms:
  - nausea, vomiting, weakness, irritable, behavior changes, poor appetite, sleepiness.

Case #3

- No pregnancy or delivery complications
- Term male, BW 7lbs 2oz
- NBS at 4 days shows C5-OH elevation (1.3umol/L, nl<0.6)
- Further studies confirm 3MCC deficiency
- Maternal testing normal
- At 14 wks baby growing well, mild spitting up

3MCC deficiency

- In the past the diagnosis was made in children being evaluated for other clinical reasons.
- Some healthy affected mothers were diagnosed after their babies positive newborn screen.
- Is it a diagnosis without a disease??

Cobalamin C deficiency
Cobalamin C deficiency

- Organic acid oxidation disorder involving vitamin B12 - CblC, CblD, CblF
- Positive screen may indicate maternal B12 deficiency in up to 50% of cases
- Symptoms within the 1st year, often by 1 mo
- Rare cases of adult onset
- A small number of affected individuals may never develop symptoms

Cbl C deficiency - Symptoms

- Clinical:
  - Poor appetite and growth
  - Lethargy, low muscle tone
  - Microcephaly
  - Brain anomalies
  - Seizures
  - Dev delay
  - Vision, heart, kidney problems
- Laboratory:
  - High levels of homocysteine and methylmalonic acid in blood and urine
  - Metabolic acidosis
  - Anemia
  - Low platelets
  - Low white blood count

Case#4

- Female 2565 gm near term
- Emergency C-section with meconium staining
- Possible pneumonia vs meconium aspiration
- Poor feeding, some posturing
- Abnormal 1st NBS at day 8 with C3 = 11.88 (nl < 6.92), C3/C2 = .62 (nl < .2), possible methylmalonic or propionic acidemia
- On day 8 poor feeding but improving, mild intermittent arching

Case#4 (cont)

- Blood draw for diagnostic testing unsuccessful
- Transfer to NICU on day 11: pale, dry, hypertensive, posturing and arching, low WBC, low platelets
- Stabilized
- Transfer to major center on day 13
- Lab studies consistent with defect in B12 metabolism probably CblC deficiency
- Day 20 stable with feeding issues, discharge in 2 weeks

Conclusion

- Expanded NBS ensures early detection of several metabolic diseases
- NBS is a screen
- A positive screen does not always mean disease
- A positive diagnosis does not always mean a disease
- The implication of a disease diagnosis made through NBS vs one made later for specific clinical indications may not be the same
- Genes interact with each other and the environment
- Follow-Up Program tracks positive newborn screens to assist in recommendations for diagnostic labs and management
- Follow-Up Program provides a local resource for families