Inborn Errors of Metabolism

Michael J. Gambello, MD, PhD
Associate Professor of Human Genetics

Specific Objectives

• Understand the basics of inborn errors of metabolism (IEM).

• Recognize the common presentations and treatments of IEM

• Recognize the proper laboratory testing for a suspected IEM

Archibald Garrod 1857-1936

• 1892 – Discovers hematoporphyrin in urine of patient with chorea
• 1902 – Lancet paper on alkaptonuria & chemical individuality
• 1908 – Concept of Inborn Errors of Metabolism (IEM)
  – Albinism
  – Alkaptonuria
  – Cystinuria
  – Pentosuria
• Variations are congenital & due to Mendelian inheritance
The Treasure of Exceptions

Archibald Garrod – Father of inborn errors of metabolism

"Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature by careful investigation of cases of rare forms of disease. For it has been found, in almost all things, that what they contain of useful or applicable nature is hardly perceived unless we are deprived of them, or they become deranged in some way."

His contemporary Bateson coined phrase:
"Treasure your exceptions"

Asbjørn Følling – Discovers PKU

- 1934 – Borgny & Harry Egeland seek help for 2 children with severe ID & musty odor to their urine
- Følling performs urine screening and using ferric chloride notes an unusual dark green color
- Identifies elevated phenylpyruvate (phenylketonuria) – from elevated phenylalanine.

Father Newborn Screening

1962 Robert Guthrie

Bacterial inhibition assay for purine and pyrimidine metabolites in cancer
**Basic Principles**

- Most inborn errors are defects in ENZYMES or TRANSPORTERS.
- Phenylalanine hydroxylase
- Carnitine transporter
- Enzymes and transporters are proteins that are encoded by genes.

**Basic Principles**

- Almost all are AUTOSOMAL RECESSIVE.
- A mutation is required on both copies of the gene.
- Typically enzyme activity <5% of normal
- Parents are obligate carriers
- 25% Recurrence risk
- X-Linked Disorders.
  - OTC Deficiency
  - Hunter syndrome
  - Fabry disease

**Basic Principles of Inborn Errors**

- Elevated A/B ratio
- Toxic Effects of A and its byproducts
- Effects of too little B
- Mutations in Enzyme or Cofactor
Daunting Number of Enzymes and Pathways

Classification

- Energy Metabolism
  - Protein
  - Fats
  - Carbohydrates

- Organelle Dysfunction
  - Lysosomal storage
  - Mitochondrial
  - Peroxisomal

Metabolism = Anabolism and Catabolism

- Protein
- Amino Acids
- Phenylyalanine
- Leucine
- Valine
- Isoleucine
- Methionine
- Etc.

- Make Biomass
  - Muscle, other Molecules etc.

- Unused degraded (enzymes)
  - For Energy

- Krebs Cycle
Presentation

Can see mild, attenuated forms: Developmental delay, psychiatric disease, intermittent mental status changes, epilepsy, hypotonia. If you think of the possibility of an IEM, test for them – EVEN WHEN THERE IS A NEGATIVE NBS!

Basic Laboratory Evaluations

- Electrolytes - especially bicarbonate to evaluate acid base status and anion gap.
- Blood glucose - ALL children with mental status change, seizure, acute illness.
- Ammonia – Acute encephalopathy, mental status changes. Mainly seen in urea cycle defects, organic acidemias.
- Ammonia – Free flowing specimen when possible, on ice to lab quickly!
- Elevated levels should be confirmed. Sometimes arterial sample.
- Levels above 300 μmol/L, nephrology should be called for emergent dialysis – as well as neighborhood metabolic MD.

Basic Laboratory Evaluations

- Urine Ketones
  - Prominent features of organic acidemias.
  - Fatty acid oxidation disorders hypoketotic hypoglycemia
- Plasma Lactate
  - Most commonly marker of hypoxia and poor perfusion.
  - Elevated levels associated with mitochondrial disease, GSD1A.
Basic Laboratory Evaluations

- Plasma Amino Acids
  - Specific elevations seen in amino acidopathies.
    - PKU
    - MSUD
    - Urea cycle disorder
- Urine Organic Acids (RARELY URINE AMINO ACIDS)
  - Methylmalonic acid
  - Propionic acid

Basic Laboratory Evaluations

- Plasma Acylcarnitine and Carnitine

Aminoacidopathies

- Phenylketonuria
- Maple Syrup Urine Disease (MSUD)
- Tyrosinemia
Phenylketonuria - PKU

Two Mutations (pathogenic variants) in Phenylalanine Hydroxylase

Phenylalanine Hydroxylase

<table>
<thead>
<tr>
<th>TOXIC EFFECTS OF TOO MUCH PHE</th>
<th>EFFECTS OF TOO LITTLE TYR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated Phe/Tyr ratio</td>
<td>Tyr required for synthesis</td>
</tr>
<tr>
<td>Toxic to Developing AND Adult Brain</td>
<td>Of dopamine, norepinephrine, epinephrine</td>
</tr>
</tbody>
</table>

Autosomal Recessive

1/10,000 (carrier frequency 1/50) -
False Positives due to TPN (Phe/Tyr ratio helps)
NO CLINICAL SYMPTOMS IN NEWBORN PERIOD.
Enough to grow (essential AA) but maintain low levels
Filter Paper Monitoring
Kuvan – BH4 analogue
Definitive diagnosis:
- Plasma Amino Acid Analysis
- DHPR testing and urine pterins

Maternal PKU

- IMPORTANT FOR YOUR ADOLESCENT GIRLS WITH PKU
- Elevated phenylalanine during pregnancy is teratogenic
- Good dietary control required BEFORE pregnancy (2-6 mg% = 120-360 μmol/L)
- Normal Blood Phe < 120 μmol/L
- Elevated MATERNAL Phenylalanine levels associated with:
  - Microcephaly
  - IUGR
  - Intellectual disability
  - Congenital heart defects
**Maple Syrup Urine Disease (MSUD)**

**KetoAcids**

- Leu
- Val
- Iso

**Thiamine**

** Decreased Products for Energy Production**

**Branched Chain Ketoacid Dehydrogenase**

Leucine particularly toxic to the brain

---

**MSUD**

- **Autosomal Recessive**
- Characteristic maple odor (urine and cerumen).
- Diet vs Hemodialysis to reduce leucine and branched chain amino acids quickly.
- Cerebral edema dreaded complications

- **Classic / Neonatal** – Poor feeding, lethargy, coma, apnea. Can present BEFORE NBS
- Intermediate – Poor growth, irritability, developmental delay
- Intermittent – Normal growth and development, episodic decompensations

---

**MSUD**

- **Diagnosis:** Plasma amino acids
  - Elevated Leucine, Isoleucine and valine.
  - Allo-Isoleucine
- DNA confirmation.
- In acutely lethargic in differential diagnosis.
- Can measure urine ketones if very high worrisome.

- **Treatment**
  - Balance between branch chain free formula (Ketonex-1 and Ketonex-2) and Natural protein (branched chains are essential Aas).
  - Supplement with isoleucine and valine.
  - Balance growth vs. Too much BCAA.
  - Exfoliative dermatitis if BCAA too low.
  - Thiamine
  - Liver Transplantation
**Transient Tyrosinemia of the Newborn**

- One of the most common amino acid disorders
- Late fetal maturation of 4-hydroxyphenylpyruvate dioxygenase
- More common in premature infants
- Asymptomatic
- Tyrosine as high as 2000 µmol/L
- Protein restrict, 2g/kg/day – Vitamin C
- Resolves 4-6 weeks

Manning K. et al. PNAS; 1999; 96:11928-11933

**Tyrosinemia-Type 1**

- Autosomal Recessive due to deficient fumarylacetoacetate hydrolase. 1/100,000
- Hepatic Failure, Fanconi syndrome
- Cirrhosis, Carcinoma
- Diagnosis: Tyrosinemia Type 1 Plasma amino acids and urine succinylacetone.
- DNA confirmation.
- Treatment revolutionized with discovery of NTBC.

Manning K. et al. PNAS; 1999; 96:11928-11933

**Organic Acidemia**

- Methylmalonic Acidemia

http://flipper.diff.org/apptagsaccount/items/5453
Isolated Methylmalonic Acidemia

Valine  Isoleucine  Threonine  Methionine  Odd chain fatty acids  Cholesterol

MethylmalonylCoA Mutase  AdoCbl  Succinate-CoA

Methylmalonic Acidemia

- Defect in methylmalonyl CoA Mutase, a defect in transport or synthesis of its cofactor adenosyl cobalamin, or of another enzyme methylmalonyl epimerase. All autosomal recessive.
- Severe Neonatal Onset, lethargy, coma to milder adult forms
- Metabolic Acidosis, Anion Gap.
- Hyperammonemia
- Neutropenia, Thrombocytopenia
- Hyperglycinemia

Methylmalonic Acidemia

- Diagnosis:
  - Acylcarnitine profile (elevated C3 carnitines)
  - Urine organic acids – methylmalonic acid
  - Plasma amino acids - Elevated glycine
  - Homocysteine - Normal
  - B12 – Deficiency can cause elevated MMA
  - DNA confirmation

- Treatment:
  - Diet
  - Carnitine
  - B12
The Urea Cycle

- Purpose: To facilitate the elimination of ammonia waste ($\text{NH}_4$) by conversion to the water soluble urea that can be eliminated in the urine.
- Defects in all the enzymes of this cycle have been reported.
- Most result in plasma ammonia levels > 150µmol/L.
- Important Consideration in Differential Diagnosis of Neonatal Encephalopathy and ANY altered mental status.
Ornithine Transcarbamylase Deficiency

Classic Urea Cycle Defect Affect Male Infants severely –
X-LINKED BUT females can manifest milder, clinically significant disease.

Normal for 24-48 hours,
Poor feeding, grunting, lethargy (sepsis), coma, occasionally cerebral edema

Ammonia usually > 700 μM/L
Orotic Acid elevated in urine

Affected first-born males usually die, or severely impaired.

IMPORTANT to make MOLECULAR (DNA) diagnosis. Can offer prenatal testing.

OTC Deficiency

• Low-Protein Diet
• Medical Food
• Ammonia scavenging drugs
  – Phenylbutyrate
  – Glycerol phenylbutyrate
• Arginine
• Dialysis in acute decompensation
• Liver transplantation in boys

Citrullinemia

• Autosomal recessive defect in Argininosuccinate synthase 1
• Very high levels of citrulline
• Typical neonatal hyperammonemic crisis
• Orotic acid elevated but not as high as OTC, arginine low.
• Arginine an important part of management
• Liver transplantation

**Arginase Deficiency**

- Autosomal recessive disorder of arginase.
- Quite different from all other urea cycle defects.
- Presentation is not typically neonatal hyperammonemia, but spastic quadriplegia (CP) and delayed milestones.
- Arginine levels high.

**Classic Galactosemia**

- Autosomal recessive disorder of galactose metabolism.
- Lactose (disaccharide of galactose and glucose)
- GALT (galactose-1-phosphate uridyltransferase) activity is less than 5% of normal.
- Diagnosis: RBC GALT activity and DNA confirmation.

**Classic Galactosemia 270 Symptomatic Neonates**

- Jaundice 74%
- Hepatomegaly 43%
- Abnormal LFTs 10%
- Coagulation Abn 9%
- Ascites 4%
- Vomiting 47%
- Diarrhea 12%
- Poor Feeding 23%
- FTT 29%
- Lethargy 16%
- Sepsis 10%
  - (Most often E. Coli.)

Waggoner et al. 1990
### Galactosemia

- Renal Fanconi syndrome
- Reducing substances neither sensitive nor specific.
- Untreated leads to intellectual disability, cataracts, liver failure and death.
- Discontinue all lactose diet, including breast feeding, and switch to soy formula.
- In spite of treatment, patients can still have cognitive effects.
- Females at risk of premature ovarian failure.

### Fatty Acid Oxidation Disorders

- Fatty acids provide ca. 80% energy in fasting states.
- Beta oxidation in the mitochondria shortens the carbon chains by 2, producing Acetyl CoA to enter Krebs cycle.
- Products are used to generate ATP and ketone bodies, 3-Hydroxybutyrate and acetoacetate for terminal oxidation.
- In early infancy, FAO Defects usually present as acute life threatening episodes of hypoketotic, hypoglycemic crises usually induced by fasting or febrile illness.
- CPK and uric acid often elevated and can be important clues for the diagnosis of FAO Disorders.
- Dicarboxylic aciduria common.

### MCAD Deficiency

- Autosomal recessive defect in Medium Chain Acyl CoA Dehydrogenase
- Most common Fatty Acid Oxidation Disorder, 1/6000-10,000.
- Presentations
  - Hypoketotic hypoglycemia, Reye-like illness usually with intercurrent illness causing fasting.
  - Myopathy, cardiomyopathy
  - SIDS
- Newborn Screening successful in identifying babies before first episode.
- Diagnosis:
  - Elevated C10, C10:1, C8, C6, and C6/C8:1 and C10:1/C10 on Acyl Carnitine Profile
  - DNA confirmation
Treatment of MCAD

- AVOID FASTING!!!
- Treatment with iv glucose (D10) when fasting during intercurrent illness.
- Supplemental carnitine.

Acute Management

Summary

- IEM are usually recessive defects in enzymes that result in the accumulation of metabolites, and too little products.
- Acute presentation: Lethargy, vomiting, poor feeding, hypotonia, coma.
- Milder presentations are not uncommon and frequently missed. Think of IEM and send testing.
- Basic testing: Electrolytes, plasma amino acids, urine organic acids, acylcarnitine and carnitine profile – A good start.
- We are always available to answer your questions: 404-686-5500 x50263