INBORN ERRORS OF METABOLISM, PART 1
I have no relevant financial relationships to disclose or conflicts of interest to resolve.

I will not discuss any unapproved or off-label, experimental or investigational use of a product, drug or device.
LEARNING OBJECTIVES

1. Describe inborn errors of metabolism in neonates
2. Discuss methods for early recognition and treatment of neonates with inborn errors of metabolism
3. Review differential for metabolic encephalopathy in the newborn.
4. Discuss advances in neonatal care of patients with inborn errors of metabolism
Inborn errors of metabolism are inherited biochemical disorders with specific enzyme defect that interferes with the normal metabolism of protein, fat or carbohydrate.

- **Subgroups**
  - Disorders of Protein metabolism
    - Disorders of Amino Acid Metabolism
    - Urea Cycle Defects
    - Organic Acidemias
  - Disorders of Carbohydrate Metabolism
    - Lysosomal Storage Defects
    - Peroxisomal Disorders
    - Endocrine Disorders
    - Fatty Acid Oxidation
    - Mitochondrial Disorders
Newborn Screening was established in 1963
- Considered the most successful public health initiative in the nation
- 1 in 300 newborns have a condition detectable by newborn screen

Florida currently screens for 36 conditions
- This includes about 20 metabolic disorders

Blood testing results for metabolic tests are usually ready within 5 days after the sample is collected

NOTE: Parents have the option to OPT OUT of newborn screening
WHEN TO CONSIDER ... INBORN ERRORS OF METABOLISM

- Normal infant at birth (usually term)*
- Illness presentation within first 48 hours of age

FAMILY HISTORY
- Neonatal death of unclear etiology
- History of child with neurologic deterioration
- History of multiple miscarriages
- Consanguinity

CLINICAL PRESENTATION
- Poor oral intake &/or vomiting
- Lethargy coma, seizures, changes in tone or reflexes
- Hepatosplenomegaly, dysmorphic features
- Cataracts
Emergent Management
1. Stop all enteral feeds to eliminate protein, galactose and fructose
2. Change IV fluids to D10 to deliver GIR 8-10 mg/kg/min. Discontinue IV lipids
   - Even if insulin is required to maintain blood glucose
3. Treat any significant acidosis (pH < 7.22)
4. Eliminate toxic metabolites
   - Ammonia < 500 μM/L → Sodium Benzoate OR Phenylacetate
   - Ammonia > 500 μM/L → Hemodialysis
5. Consult Genetics
Differential includes an inborn error of metabolism

**Primary Evaluation**
Send the following laboratory test...
- CBC with differential
  (neutropenia or thrombocytopenia)
- Electrolytes and arterial blood gas (acidosis, alkalosis, increased anion gap)
- Glucose assess presence or absence of ketones
- Plasma ammonia concentration*
- Lactate and pyruvate concentrations with ratio of lactate to pyruvate
- Liver function tests
- Urine ketones
- Check newborn screen, if available

**Secondary Evaluation**
- Plasma amino acid analysis
- Urine organic acid analysis
- Plasma carnitine and acylcarnitine
- Plasma uric acid
- CSF amino acid analysis
- Peroxisomal function test

Geneticist will likely recommend:
# Inborn Errors of Metabolism: Lab Findings

<table>
<thead>
<tr>
<th>Anion Gap Metabolic Acidosis</th>
<th>Respiratory alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organic Acidemias</strong></td>
<td><strong>Urea cycle defects</strong></td>
</tr>
<tr>
<td>Propionic, Isovaleric and Methylmalonic Acidemia</td>
<td></td>
</tr>
<tr>
<td><strong>Fatty Acid Oxidation, Short, medium long chain abnormalities</strong></td>
<td><strong>Normal Anion Gap</strong></td>
</tr>
<tr>
<td>Carnitine Deficiency</td>
<td></td>
</tr>
<tr>
<td><strong>Congenital Lactic Acidosis</strong></td>
<td><strong>Neutropenia &amp; Thrombocytopenia</strong></td>
</tr>
<tr>
<td>Pyruvate Dehydrogenase, Mitochondrial Disorders of Respiratory Chain</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Lactic Acidosis</strong></td>
<td><strong>Organic acidemias, glycogen storage disease type I, organic acidemias</strong></td>
</tr>
<tr>
<td>Hereditary fructose intolerance, <strong>glycogen storage disease type I, organic acidemias</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td><strong>Ammonia</strong></td>
</tr>
<tr>
<td>Prematurity (liver failure from TPN), <strong>HIE</strong>, severe hepatitis, abnormal mitochondrial oxidation from hypoxia</td>
<td></td>
</tr>
<tr>
<td><strong>Organic acidemias, urea cycle defects</strong>, transient ammonia of the neonate</td>
<td></td>
</tr>
</tbody>
</table>
An newborn infant present with lethargy and poor feeding in the first day of life. Negative infectious work up. Head imaging shows no evidence of IVH, stroke or mass. Serum ammonia is 300 μM/L with normal concentrations of lactate and amino acid. The urine does not contain ketones and has normal organic acid levels.

Of the following, the infant in this vignette most likely has:

A. Arginase Deficiency (Urea Cycle Defect)
B. Glutaric Aciduria (Disorder of Protein Metabolism)
C. Methylmalonic Acidemia (Organic Acidemia)
D. Ornithine Transcarboxylase Deficiency (Urea Cycle Defect)
E. Transient Neonatal Hyperammonemia
# Inborn Errors of Metabolism

<table>
<thead>
<tr>
<th>Carbohydrate Metabolism Disorder</th>
<th>Organic Acid Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galactosemia</td>
<td>Propionic Acidemia</td>
</tr>
<tr>
<td>Glycerol Kinase Deficiency</td>
<td>Isovaleric Acidemia</td>
</tr>
<tr>
<td>Glycogen Storage Diseases</td>
<td>Methylmalonic Acidemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amino Acid Disorders</th>
<th>Urea Cycle Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylketonuria</td>
<td>CPS Deficiency</td>
</tr>
<tr>
<td>Tyrisonemia</td>
<td>OTC Deficiency</td>
</tr>
<tr>
<td>Maple Syrup Urine Disease</td>
<td>Citrillinemia</td>
</tr>
<tr>
<td>Nonketotic Hyperglycinemia</td>
<td>Argininosuccinic Aciduria</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>Argininemia</td>
</tr>
<tr>
<td>Glutaric Acidemia Type I</td>
<td></td>
</tr>
<tr>
<td>Inborn Errors of Metabolism Categories</td>
<td>Incidence/Inheritance</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Disorders of Carbohydrate Metabolism</td>
<td></td>
</tr>
<tr>
<td>Galactosemia</td>
<td>1:40,000 AR</td>
</tr>
<tr>
<td>Glycogen Storage Disease (Von Gierke)</td>
<td>1:100,000 AR</td>
</tr>
<tr>
<td>Phenylketonuria (PKU)</td>
<td>1:15,000 AR</td>
</tr>
<tr>
<td>Maple Syrup Urine Disease</td>
<td>1:150,000 AR</td>
</tr>
<tr>
<td>Tyrosinemia type I</td>
<td>Rare AR</td>
</tr>
<tr>
<td>Glutaric Acidemia</td>
<td>1:30-40,000 AR</td>
</tr>
<tr>
<td>Urea Cycle Defects</td>
<td>1:30,000</td>
</tr>
</tbody>
</table>
CARBOHYDRATE METABOLISM DISORDERS
7 day old female infant transferred from OSH for evaluation of poor feeding, vomiting and abdominal distention. Required treatment for hyperbilirubinemia (total bili 15.4) at 4 days of life. Labs prior to NICU admission were normal except mild transaminitis (AST 156 and ALT 188 U/L) and transient elevation in ammonia (202 µg/dl). Ammonia normal when rechecked on admission. Sepsis work up was negative.

**Birth History:** Born at 37 weeks GA via SVD. Of note, mother had epilepsy, which was treated with Carbamazapine throughout pregnancy.

**NICU Management:** For 9 days, low-protein, lactose-free, hydrolysate formula due to concern for cow’s milk intolerance. Progressive clinical improvement and normal labs. At the age of 16 days, a standard formula feeding was re-introduced, still with a reduced intake of proteins. Again, vomiting and anorexia occurred, further supporting the hypothesis of cow’s milk intolerance. Thus, the same protein hydrolysate formula used earlier was resumed and continued in the following months.

Which metabolic disorder should also be considered?

Casa et al, 2012
- **Autosomal recessive** disorder of galactose metabolism
- 1/40,000 live births in the US

- **Three forms:** Classic galactosemia, Galactokinase deficiency, Galactose-4’-epimerase deficiency

- **Screening** (Most US states use a combination of these approaches)
  - Measures GALT activity* &/OR Galactose and Galactose-1-Phosphate

- **Clinical Presentation:** Lethargy, poor feeding, jaundice, cataracts, *E. coli* sepsis

- **Laboratory findings:** ↓glucose, ↑LFTs, ↑total bilirubin, hyperchloremic metabolic acidosis*, normal lactate, normal pyruvate

- **Diagnostic Test**
  - Urinary reducing substances*
  - Whole blood or erythrocyte GALT activity and erythrocyte red cell galactose-1-phosphate

- **Treatment:** Strict dietary lactose /galactose restriction

- **Long term Prognosis:** Mild growth failure, learning disabilities, ataxia, tremor and verbal dyspraxia
  - Ovarian failure, probable infertility in males also
GALACTOSEMIA PATHWAY

Diagnosis in Absence of Enzyme

1. Lactose intolerance
2. Galactokinase
3. Classic Galactosemia
4. Galactose-4' Epimerase Deficiency

- Lactose intolerance
- Galactokinase
- Classic Galactosemia
- Galactose-4' Epimerase Deficiency

Cataracts, FTT, diarrhea, jaundice, intellectual disability and liver failure (first few months of life)
GLYCEROL KINASE DEFICIENCY

- **X-linked recessive** defect in glycerol kinase
- **FL State Newborn Screen NO**
- **Clinical Presentation:** Can present in neonatal period: cryptorchidism, seizures, strabismus.
  - Isolated Symptomatic: Lethargy, vomiting, acidosis, ketotic hypoglycemia
  - Isolated Benign
  - **Complex (Deletion Syndrome):** Glycerol Kinase Deficiency, Adrenal Hypoplasia and Duchenne Dystrophy
- **Lab Findings:** Pseudotriglyceridemia (elevated glycerol interferes with assay for triglycerides)
- **Diagnostic studies:** FISH analysis to assess for deletion
  - Glycerol kinase gene near dystrophin and congenital adrenal hypoplasia gene
- **Treatment:** Manage SYMPTOMS as indicated by using corticosteroids, glucose infusion, or mineralocorticoids
  - No permanent treatment available
- **PROGNOSIS:** Infantile form is associated with severe developmental delay
<table>
<thead>
<tr>
<th>Type</th>
<th>Enzyme defect</th>
<th>Eponym</th>
<th>Hypoglycemia</th>
<th>Hyperlipidemia</th>
<th>Symptoms</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSD type 1</td>
<td>Glucose-6-phosphatase</td>
<td>Von Gierke's</td>
<td>Yes</td>
<td>Yes</td>
<td>Growth failure</td>
<td>Lactic acidosis, hyperuricemia</td>
</tr>
<tr>
<td>GSD type 2</td>
<td>Acid maltase</td>
<td>Pompe's</td>
<td>No</td>
<td>No</td>
<td>Death by age ~2 years</td>
<td>Heart failure, Myopathy</td>
</tr>
<tr>
<td>GSD type 3</td>
<td>Glycogen debrancher</td>
<td>Cori's or Forbes'</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Myopathy</td>
</tr>
<tr>
<td>GSD type 4</td>
<td>Glycogen branching enzyme</td>
<td>Andersen</td>
<td>No</td>
<td>No</td>
<td>Failure to thrive, death at age ~5 years</td>
<td>Liver cirrhosis</td>
</tr>
<tr>
<td>GSD type 5</td>
<td>Muscle glycogen phosphorylase</td>
<td>McArdle</td>
<td>No</td>
<td>No</td>
<td></td>
<td>Renal failure by myoglobinuria</td>
</tr>
<tr>
<td>GSD type 6</td>
<td>Liver glycogen phosphorylase</td>
<td>Hers’ disease</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSD type 7</td>
<td>Muscle phosphofructokinase</td>
<td>Tarui’s disease</td>
<td>No</td>
<td>No</td>
<td>Growth retardation</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>GSD type 9</td>
<td>Phosphorylase kinase PHKA2</td>
<td></td>
<td></td>
<td>Yes</td>
<td>Delayed motor development, growth retardation</td>
<td></td>
</tr>
<tr>
<td>GSD type 11</td>
<td>Glucose transporter GLUT2</td>
<td>Fanconi-Bickel Syndrome</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSD type 12</td>
<td>Aldolase A</td>
<td>Red cell aldolase deficiency</td>
<td>?</td>
<td>?</td>
<td></td>
<td>Exercise intolerance</td>
</tr>
<tr>
<td>GSD type 13</td>
<td>B-enolase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Glycogen → Glycogen  

Glycogen → Glycogen  

Glucose 1-phosphate → Phosphoglucomutase  

Glucose 6-phosphate → Glycolysis (Muscle, brain)  

Glucose 6-phosphate → Liver (Glucose 6-phosphatase)  

Glucose 6-phosphate → Pentose Phosphate Pathway  

Glucose → Lactate  

Glucose → CO₂ + H₂O  

Glucose → Ribose + NADPH  

Glucose → Blood for use by other tissues
Autosomal recessive defect in glucose-6-phosphatase → glycogen accumulates in the liver

FL State Newborn Screen NO

Clinical Presentation: Normal at birth. Hypoglycemia presents when infants start to sleep through the night (prolonged fasting). Hepatomegaly
  - May present in neonatal period

Lab Findings: Hypoglycemia, lactic acidosis, ↑urea, ↑ lipids and triglycerides

Diagnostic studies
  - Liver biopsy glycogen and assay for enzyme
  - DNA testing may obviate need for liver biopsy

POMPE DISEASE (GSD 2)

- **Autosomal recessive** disorder of α 1,4-glucosidase
- **FL State Newborn Screen** NO
- **Clinical Presentation**: Normal at birth. Then onset of muscle weakness, feeding and breathing difficulty
  - Infantile: dilated cardiomyopathy, failure to thrive, hypotonia, macroglossia
- **Lab Findings**: NO hypoglycemia!!!, ↑CPK
- **Diagnostic studies**: Assay enzyme in lymphocytes, muscle or fibroblasts
- **Treatment**: Enzyme Replacement Therapy available since 2006
An infant presents in the newborn period with lactic acidosis, hypoglycemia and hepatomegaly. Further testing reveals the infant has glycogen storage disease.

Of the following, the enzyme that is most likely to be deficient in this infant is:

A. Branch enzyme  
B. Debranching Enzyme  
C. Glucose-6-Phosphate  
D. Lysosomal Alpha-Glucosidase  
E. Phosphorylase kinase
- **Autosomal recessive** disorder in which phenylalanine can not be converted to tyrosine
- 1/10-20,000 live births in the US
- **Enzyme Defect:** Phenylalanine Hydroxylase (chromosome 12q24.1)
- **Clinical Presentation:** Normal at birth. >50% affected infants present with the following signs:
  - Vomiting, irritability, eczematoid rash, peculiar odor ‘musty’, fair-hair and skin
- **Screening** (In all 50 states)
  - Test for elevated levels of phenylalanine
- **Diagnostic studies**
  - If positive screen, quantitative analysis of serum phenylalanine and tyrosine
- **Treatment:** Limit dietary intake of phenylalanine.
  - Followed by dietician and Phe levels are monitored closely
- **Long term Prognosis:** If untreated severe intellectual disability IQ < 30. Acquired microcephaly
  - Damage becomes irreversible by 8 weeks of age
<table>
<thead>
<tr>
<th>Enzyme Defect</th>
<th>Clinical Presentation</th>
<th>Diagnostic Studies</th>
<th>Treatment</th>
<th>Prognosis</th>
<th>FL State Newborn Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong></td>
<td>Failure to thrive (FTT)</td>
<td>Succinylacetone in urine↑</td>
<td>Diet low in tyrosine and phenylalanine-NTBC</td>
<td>Infants are affected early with high risk of mortality</td>
<td>Yes</td>
</tr>
<tr>
<td>Fumarylacetoacetate hydroxylase</td>
<td>Hepatomegaly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatoblastoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RTA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rickets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type II</strong></td>
<td>Corneal ulcers or dendritic keratitis</td>
<td></td>
<td>Diet low in tyrosine</td>
<td>Diet may not be curative</td>
<td>Yes</td>
</tr>
<tr>
<td>Tyrosine Aminotransferase</td>
<td>50% with intellectual disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Red papular lesions on their palms and soles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No liver toxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Autosomal recessive disorder of branched chain amino acid metabolism (valine, leucine and isoleucine)

~ 1/150,000 live births in the US (1:1000 Mennonites)

Enzyme Defect:
- Defect in oxidative decarboxylation of ketoacids

FL State Newborn Screen YES

Clinical Presentation: Feeding difficulty, irregular respirations, loss of Moro reflex, bicyclic motion of legs/swimming with arms, severe seizures, opisthotonos and rigidity

Diagnostic Test
- Plasma amino acid: ↑ leucine, isoleucine & valine
- Urine organic acids – branched chain 2-keto and 2-hydroxy acids
- Presence of alloisoleucine is diagnostic

Treatment: Strict dietary control of leucine, isoleucine and valine restriction
- Rare form that responds to Thiamine

Long term Prognosis:
- Rapid progression to death within 2-4 weeks in no treatment initiated
- If early therapy normal IQ is possible
A CASE TO REMEMBER

- A 7-month-old female is transferred from OSH for further evaluation of persistent seizures and dystonia following acute pyogenic meningitis.
- She was diagnosed with meningitis after presenting with fever, vomiting, irritability, and generalized seizures
  - CSF fluid analysis: 8 WBC cells/μL (All Lymphocytes), Protein 52 g/dl, and Glucose 62 mg/dl.
  - OSH CT brain bilateral arachnoid cyst
- BIRTH HISTORY: Born term via SVD was
- DEVELOPMENTAL HISTORY: Reaching milestones appropriately

What additional information is needed?
**GLUTARIC ACIDEMIA TYPE 1**

- **Autosomal recessive** disorder resulting in defect in the catabolic pathway of lysine, hydroxylysine and tryptophan
- 1/30-40,000 live births in the US
- **Enzyme Defect:** Glutaryl-CoA Dehydrogenase (on chromosome 19)
- **FL State Newborn Screen:** YES
- **Clinical Presentation:** Macrocephaly at birth, normal development until illness or metabolic stressor → hypotonia and dystonia ‘mimics acute onset CNS infection’
  - CT/MRI brain findings are present at birth (see images next)
  - Can cause subdural hematomas and retinal hemorrhages
- **Diagnostic Test**
  - Urine organic acids: ↑ glutaric acid and 3-hydroxyglutaric acids
  - Plasma carnitine levels are low
  - Prenatal diagnosis: increased concentrations of glutaric acid in amniotic fluid – DNA test preferred
- **Treatment:** L-carnitine, riboflavin and special diet
  - When acutely ill provide IV fluids containing glucose
- **Long term Prognosis:** Mild growth failure, learning disabilities and verbal dyspraxia
  - 5% of patients will be asymptomatic
  - 35% of patients will have severe disease despite optimal therapy
GLUTARIC ACIDEMIA TYPE 1

Protein from food → Protein from muscles → Amino Acids → Tryptophan + Lysine → Other Amino acids → Glutaric acid

Glutaryl-CoA dehydrogenase enzyme

Build up of Glutaric acid & 3-OH GA + other harmful substances → Health Problems

Energy → Growth
- **Autosomal recessive** disorder of methionine metabolism
- 1/200-335,000 live births worldwide
  - Ireland (1 in 65,000), Germany (1 in 17,800), Norway (1 in 6,400), and Qatar (1 in 1,800).
- **Enzyme Defect:** Cystathionine β-synthetase (chromosome 21q)
- **Screening** YES (Elevated methionine)
- **Clinical Presentation:** Marfanoid habitus, developmental delay, downward /medial lens dislocation, osteoporosis and increased risk of arterial/venous thromboembolism
  - Presents within first 10 years
- **Diagnostic Test**
  - Blood and urine test for excess homocysteine and methionine. Low level of cysteine
  - Liver biopsy and enzyme assay for enzymatic activity
- **Treatment:** Large doses of pyridoxine (B6), B12 and folic acid. Diet low in methionine
  - Supplementation with Betaine
- **Long term Prognosis:** Intellectual disability is fairly common
2-day-old male infant is transferred from Newborn Nursery with lethargy, poor feeding, and frequent hiccups.

**Birth History:** Born at term via SVD. Pregnancy was uneventful.
- Birth weight - 3.2 kg (50th %ile) and Head circumference - 35 cm (50th %ile)

**Admission Examination:** Gross hypotonia, poor suck, weak cry and no dysmorphic features.

**NICU course:**
- ** Apneic episodes** requiring ventilatory support. No spontaneous breathing was observed while on ventilator despite not being on sedation.
- Later noted to have some abnormal movements including jitteriness, hiccups, and twitching of his limbs for which he was treated with phenobarbitone.

1. Create a Differential Diagnosis.
2. Order laboratory test to narrow the Differential.
- **Autosomal recessive** disorder of glycine metabolism
- 1/250,000 in the US
- **Enzyme Defect:**
  - More than 80% of patients have a defect in P-protein of glycine cleavage enzyme
- **Clinical Presentation:** Neonatal hiccups, myoclonic seizures and altered consciousness
  - Neonatal: presents in 1st week of life
  - Infantile: presents by 6 months of age. Seizures
  - Late onset: present 2-33 years of age. progressive spastic paraparesis, choreoathetosis, and optic atrophy
- **Screening** (Most US states use a combination of these approaches) ***
- **Diagnostic Test**
  - Hyperglycinemia and elevated CSF glycine levels in the absence of an organic acid disorder
    - CSF and plasma glycine measurements are essential for the diagnosis of NKH, CSF/plasma glycine ratio > 0.08
  - Glycine cleavage enzyme assays on liver biopsy (GOLD STANDARD)
  - Prenatal diagnosis: GCS enzyme assay in chorionic villi
- **Treatment:** Sodium Benzoate → reduce CSF glycine → Decrease seizures
  - Dextromethorphan has also been used with some success
- **Long term Prognosis:** Poor prognosis. Often fatal

Igbal et al, 2015
Odd-chain fatty acids
Cholesterol, Isoleucine, Valine, Methionine, Threonine

Alternative pathway for odd-chain fatty acid synthesis

Defective enzyme in Propionic Acidemia

Propionyl CoA

Biotin

Propionyl CoA Carboxylase

D-Methylmalonyl CoA

Methylmalonyl CoA Racemase

L-Methylmalonyl CoA

Adenosylcobalamin

Methylmalonyl CoA Mutase

Succinyl CoA

TCA cycle
**PROPIONIC ACIDEMIA**

- **Autosomal recessive** defect in propionyl CoA carboxylase
- **FL State Newborn Screen** YES
- **Clinical Presentation**: Neonatal onset: Lethargy and coma
- **Lab Findings**: ↑↑ammonia, anion gap metabolic acidosis, neutropenia, thrombocytopenia, hyperglycinemia
- **Diagnostic Test**
  - Elevated propionyl carnitine.
  - Plasma amino acid: ↑Glycine
  - Urine organic acid: ↑Methylcitrate
  - Enzyme assay on leukocytes
- **Treatment**:
  - Diet
  - Carnitine
  - Biotin (Cofactor for enzyme)
**ISOVALERIC ACIDEMIA**

- **Autosomal recessive** defect in leucine metabolism
- 1:230,000 live births

- **Enzyme Defect:** Isovaleryl-CoA dehydrogenase deficiency

- **Clinical Presentation:** "Odor of sweaty feet"
  - Onset in newborn periods – severe metabolic acidosis, ketosis with vomiting → coma and death
  - Onset in infancy (more common) – symptoms are preceded by an infection or increased protein intake
    - Subsequent chronic intermittent pancytopenia and acidosis

- **FL State Newborn Screen YES**

- **Diagnostic Test**
  - Urine organic acids
  - Prenatal diagnosis is possible

- **Treatment:**
  - **Acute:** IV glucose
  - **Chronic:** Restricting leucine intake and prescribing carnitine &/or glycine
Autosomal recessive disorder that ultimately inhibits methylmalonyl-CoA mutase function.

1/55,000 live births in the Finland

**Enzyme Defect:** Mutase deficiency and Cobalamin A, B, C, D, F and X deficiency

**Clinical Presentation:** Early: hyperammonemia, ketoacidosis and thrombocytopenia
  - Late onset: complication is renal failure and cardiomyopathy

**FL State Newborn Screen** YES

**Diagnostic Test**
  - Urine organic acids (increased methylmalonic acid and abnormal ketone bodies)
  - Elevated homocysteine levels

**Treatment:** Restriction of dietary protein. Betaine and IM B_{12} vitamin only for cobalamin C, E and some D deficiencies
  - Liver and kidney transplants may be curative
UREA CYCLE DEFECTS
## Urea Cycle Defects

<table>
<thead>
<tr>
<th>Defect</th>
<th>Incidence/Inheritance</th>
<th>Deficiency</th>
<th>Symptom Onset</th>
<th>Presentation</th>
<th>Labs</th>
<th>FL State Newborn Screen</th>
</tr>
</thead>
</table>
| **CPS Deficiency**                          | 1:70-100,000 AR       | Carbamoyl phosphate synthetase I    | By 5 days of age | Lethargy, hypotonia, vomiting and poor feeding  
Death if undiagnosed  
↑Ammonia  
↑CSF Glutamine  
Respiratory alkalosis  
Low BUN  
↑Glutamine, alanine, asparagine  
↓Citrulline  
↓Arginine  
↓Urine orotic acid | NO                      |                         |
| **Ornithine Transcarbamylase (OTC) Deficiency** | 1:70,000 X-linked (Most common) | Ornithine Transcarbamylase         | 24-48 hours    | Lethargy, hypotonia, vomiting and poor feeding  
Death if undiagnosed  
↑Ammonia  
↑CSF Glutamine  
Respiratory alkalosis  
Low BUN  
↑Glutamine, Alanine, Asparagine  
↓Citriulline  
↓Arginine  
↓Urine orotic acid | NO                      |                         |
| **Citrillinemia**                           | AR                    | Arginoinosuccinate synthetase deficiency | Late onset; preceded by stressor | ↑Ammonia  
↓Arginine | Yes                      |                         |
| **Argininosuccinic Aciduria**               | AR                    | Argininosuccinate lyase deficiency | Late onset; preceded by stressor | ↑Ammonia  
↓Arginine | Yes                      |                         |
| **Arginemia**                               | AR                    | Arginase deficiency                | Late onset; preceded by stressor | Progressive spastic diplegia, tremor, ataxia  
↑Ammonia |                         | Normal Arginine          |
CO₂ + NH₃

1. Carbamoyl Phosphate Synthase

Carbamoyl Phosphate

2. Ornithine carbamoyltransferase

Orotic Acid

3. Arginosuccinate synthase

Citrulline

L-Aspartate

L-ornithene

2. Ornithine carbamoyltransferase

Arginosuccinate

3. Arginosuccinate synthase

Arginase

4. Argininosuccinate lyase

Urea

5. Arginase

L-Fumarate

H₂O

L-Arginine
Autosomal recessive disorder of amino acid metabolism

1:150-200,000 live births.

Enzyme Defect: Carbamoyl phosphate synthetase (CPS) I

Clinical Presentation: sleepiness, poorly regulated breathing rate or body temperature, unwillingness to feed, vomiting after feeding, unusual body movements, seizures, or coma

- Severe: Onset within first few days after birth
- Mild: Onset later in life

Florida State Newborn Screen NO

Lab Findings: ↑Ammonia, ↑CSF Glutamine, Respiratory alkalosis, Low BUN, ↑Glutamine, alanine, asparagine, ↓Citrulline ↓Arginine, ↓Urine orotic acid

Diagnostic Test
- Ammonia
- Plasma and urinary organic acids

Treatment: Protein restricted diet
- Acute: If infant in a coma & plasma ammonia > 500 μM/L, hemodialysis is the only way to clear ammonia
- Chronic: High calorie, protein restricted diet with or without additional amino acids
  - Infantile onset has increasing patients undergoing liver transplants with improved outcomes

Long term Prognosis: Survival beyond newborn period: recurrence of elevated ammonia. Delayed development and intellectual disability
**ORNITHINE TRANSCARBAMYLASE (OTC) DEFICIENCY**

- **X-linked** disorder of nitrogen waste removal
- **1: 70,000** (most common Urea Cycle Defect)
- **Enzyme Defect:** Ornithine Transcarbamylase (chromosome Xp11.4)
- **Clinical Presentation:** Lethargy, hypotonia, vomiting and poor feeding. Death if undiagnosed
- **Lab Findings:** ↑Ammonia (> 700 μM/L), ↑CSF Glutamine, Respiratory alkalosis, Low BUN, ↑Glutamine, Alanine, Asparagine, ↓Citrulline, ↓Arginine, ↑Urine orotic acid (diagnostic)
- **FL State Newborn Screen NO**
- **Diagnostic Test**
  - Ammonia
  - Quantitative plasma and urinary organic acids
- **Treatment:**
  - Acute: If infant in a coma & plasma ammonia > 200 μM/L, hemodialysis is the only way to clear ammonia
  - Chronic: High calorie, protein restricted diet with or without additional amino acids
    - Infantile onset has increasing patients undergoing liver transplants with improved outcomes
- **Long term Prognosis:** Affected first born males usually die, or severely impaired.
  - Females can manifest milder, clinically significant disease.
CITRILLINEMIA

- **Autosomal recessive** defect in ASS
- 1/57,000 live births in the US
- **Enzyme Defect**: Argininosuccinate synthetase (ASS)
- **FL State Newborn Screen**: Yes (↑↑↑ citrulline)
- **Clinical Presentation**: Infants with the acute neonatal form appear normal at birth. Shortly thereafter, they develop hyperammonemia and become progressively lethargic, feed poorly, often vomit, and may develop signs of increased intracranial pressure (ICP).
- **Lab Findings**: ↑↑↑ citrulline (>1000 µmol/L) ↑ammonia (> 150 µM/L), ↑orotic acid (not as high as OTC), ↓arginine
- **Diagnostic Test**
  - Ammonia, Quantitative plasma and urinary organic acids
- **Treatment**: Arginine
  - Acute: If infant in a coma & plasma ammonia > 200 µM/L, hemodialysis is the only way to clear ammonia
  - Chronic: High calorie, protein restricted diet with or without additional amino acids
- **Prognosis**:
  - Without prompt intervention, hyperammonemia and the accumulation of other toxic metabolites (e.g., glutamine) result in increased ICP, increased neuromuscular tone, spasticity, ankle clonus, seizures, loss of consciousness, and death.
  - Children with the severe form who are treated promptly may survive for an indeterminate period of time, but usually with significant neurologic deficits.
**ARGININOSUCCINIC ACIDURIA**

- **Autosomal recessive** disorder of amino acid metabolism
- 1:70,000 live births in the US
- **Enzyme Defect:** Argininosuccinate lyase – ASL (chromosome 7)
- **FL State Newborn Screen** YES
- **Clinical Presentation:** lethargy, poor appetite, vomiting, seizures, abnormal movements, difficulty breathing (tachypnea), irritability, hepatomegaly. *Trichorrhexis nodosa*
  - **Infantile:** 24-72 hours after birth
  - **Childhood:** Late infancy or early childhood
- **Lab Findings:** ↑↑ammonia, ↓arginine, ↑↑ citrulline↑ urine orotic acid
- **Diagnostic Test**
  - Ammonia and plasma and urinary organic acids
- **Treatment:** Protein restricted diet. **Arginine supplementation**
  - **Medication to treat NH$_4^+$:** sodium benzoate (not FDA approved), sodium phenylbutyrate (FDA approved 1996), and glycerol triphenylbutyrate (FDA approved 2013).
- **Long term Prognosis:** Neurocognitive deficiencies, behavior issues such as ADHD, developmental disability and seizures
**ARGININEMIA**

- **Autosomal recessive** disorder of arginine metabolism and removal of ammonia
- **1/300,000 to 1 million individuals**
- **FL State Newborn Screen NO**
- **Enzyme Defect:** Arginase deficiency
- **Clinical Presentation:** Presents by 3 years of age
  - Lower extremity spasticity, failure to thrive, developmental delay and eventual loss of developmental milestones, intellectual disability, seizures, tremor, ataxia.
- **Diagnostic Test**
  - Ammonia
- **Treatment:** *Low protein diet*
- **Long term Prognosis:** With prompt and lifelong treatment, children with arginase deficiency may be able to live healthy lives with typical growth and learning.
  - Even with treatment, some children still have effects from high blood levels of arginine and ammonia. This can result permanent learning problems, intellectual disability or **spasticity**.
A neonate suspected of having a urea cycle defect after presenting with hyperammonemia, a primary respiratory alkalosis and a normal serum glucose. The infants' serum amino acids and urine organic acids are measured. The infant has elevated serum glutamine and alanine amounts with low serum citrulline and arginine. The infant’s urine orotic acid concentrations are low.

Of the following, the most likely enzyme that is deficient in the infant in this vignette is:

A. Arginase
B. Argininosuccinic acid synthetase
C. Ornithine carbamyl transferase
D. Carbamyl phosphate synthetase
E. N-acetylglutamate syntetase
Individually rare. However, accounts for **20% of diagnosis in sick full term infants**

- Non-specific presenting symptoms
  - Requires high index of suspicion
- Many are treatable with early recognition
- Common in certain populations
- Detailed knowledge of biochemical pathways is NOT necessary to treat patients during the initial evaluation
- Important to known which IEMs are tested on the newborn screen in your state
- **Emergent management:** Stop oral feeds, provide D10 (GIR 8-10), correct acidosis, treat severe hyperammonemia. Send initial screening labs: ABG, lactate, glucose, electrolytes, liver function (attn: bilirubin), CBC with diff. **Consult Genetics.**
- Even in cases of early neonatal death, diagnosis is important for family planning.
REFERENCES

1. The National Newborn Screening and Global Resource Center (NNSGRC) http://genes-r-us.uthscsa.edu/


http://pediatrics.aappublications.org/content/102/6/e69

Special Thanks...

Department of Pediatrics/Genetics & Metabolism
Cheryl Garganta, MD, PhD
Gustavo H.B. Maegawa MD, PhD
Jim Wynn, MD
Irina Prelipcean, MD
<table>
<thead>
<tr>
<th>Drug or Chemical</th>
<th>Disorder</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arginine</td>
<td>Selected urea-cycle disorders</td>
<td>Replenishes stores</td>
</tr>
<tr>
<td>Betaine</td>
<td>Homocystinuria</td>
<td>Removes substrate</td>
</tr>
<tr>
<td>Biotin</td>
<td>Carboxylase deficiencies</td>
<td>Serves as cofactor for pathways</td>
</tr>
<tr>
<td>Carnitine</td>
<td>Carnitine deficiency</td>
<td>Replenishes stores</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Smith-Leimli-Opitz syndrome</td>
<td>Replenishes stores</td>
</tr>
<tr>
<td>Citrulline</td>
<td>Selected urea-cycle disorders</td>
<td>Replenishes stores</td>
</tr>
<tr>
<td>Cysteamine</td>
<td>Cystinosis</td>
<td>Removes substrate</td>
</tr>
<tr>
<td>Cystine</td>
<td>Homocystinuria</td>
<td>Replenishes stores</td>
</tr>
<tr>
<td>Dichloroacetate</td>
<td>Primary lactic acidosis</td>
<td>Stimulates enzyme</td>
</tr>
<tr>
<td>Folic acid</td>
<td>Homocystinuria</td>
<td>Serves as cofactor for pathways</td>
</tr>
<tr>
<td>Imiglucerase</td>
<td>Gaucher’s disease</td>
<td>Replaces enzyme</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Propionic and methylmalonic aciduria</td>
<td>Reduces propionate absorption</td>
</tr>
<tr>
<td>NTBC*</td>
<td>Tyrosinemia</td>
<td>Blocks enzyme</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>Homocystinuria</td>
<td>Serves as cofactor for pathways</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>Glutaric acidemias</td>
<td>Serves as cofactor for pathways</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>Urea-cycle disorders</td>
<td>Removes substrate</td>
</tr>
<tr>
<td>Sodium phenylbutyrate</td>
<td>Urea-cycle disorders</td>
<td>Removes substrate</td>
</tr>
<tr>
<td>Ubiquinone*</td>
<td>Mitochondrial problems</td>
<td>Serves as cofactor for substrate</td>
</tr>
</tbody>
</table>

*NTBC = 2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3-cyclohexanedione.
*Also known as coenzyme Q<sub>10</sub>.

Source: Am J Health-Syst Pharm © 2003 American Society of Health-System Pharmacists