Inherited Disorders of the Urea Cycle

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The Urea Cycle

Metabolic pathway to excrete toxic waste nitrogen

- Convert ammonia to urea
- Full functionality in the liver
- Occurs in cytosol and mitochondria
- Proper function depends on enzymes and amino acid transporters
The Urea Cycle: Enzymes & Transporters

1) N-Acetylglutamate Synthase

2) Carbamoyl-phosphate Synthase

Acetyl-CoA

3) Ornithine Transcarbamoylase

4) Arginosuccinate Synthase

5) Argininosuccinate Lyase

6) Arginase

NH₄⁺+ATP+HCO₃⁻ → Carbamoyl phosphate → Orotic acid

Aspartate → Glutamate

Citrulline

Carbamoyl phosphate

Ornithine

Citrulline

Arginosuccinate

Ornithine

Arginine

Urea

ORNT1

Cytosol

Mitochondrion

Figure adapted with permission from Garg U, Smith LD, Heese BA, eds. Laboratory Diagnosis of Inherited Metabolic Diseases. Washington, DC: AACC; 2012:55–64. © AACC.
Disorders of the Urea Cycle

- In the US about 1 in 8,200 births
- Prevalence is 1 in 35,000
- Mortality is 24% in newborn, 11% in later onset
- Occur due to mutations in enzymes or transporters
  - Most are autosomal recessive inherited
  - One is X-linked: OTC deficiency
Disorders of the Urea Cycle II

- Present with **Hyperammonemia**
- Metabolic stress triggered
- Onset age can be variable
  - Neonatal
  - Infancy
  - Childhood/Adulthood
## Disorders of the Urea Cycle III

<table>
<thead>
<tr>
<th>Urea Cycle Disorder</th>
<th>Mutated Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) NAGS deficiency (N-AcetylGlutamate Synthetase)</td>
<td>NAGS</td>
</tr>
<tr>
<td>2) CPS deficiency (Carbamoyl-Phosphate Synthase)</td>
<td>CPS1</td>
</tr>
<tr>
<td>3) OTC deficiency (Ornithine TransCarbamoylase)</td>
<td>OTC</td>
</tr>
<tr>
<td>4a) Citrullinemia I</td>
<td>ASS1</td>
</tr>
<tr>
<td>4b) Citrullinemia II</td>
<td>SLC25A13</td>
</tr>
<tr>
<td>5) ASA (Arginosuccicinc aciduria)</td>
<td>ASL</td>
</tr>
<tr>
<td>6) Arginase deficiency</td>
<td>ARG1</td>
</tr>
<tr>
<td>7) HHH syndrome (Hyperammononemia Hyperornithemia Homocitrullinuria)</td>
<td>ORNT1</td>
</tr>
</tbody>
</table>
The Urea Cycle Disorders

1) NAGS Deficiency
   - NH₄⁺+ATP+HCO₃⁻ → N-Acetylglutamate
   - N-Acetylglutamate

2) CPS Deficiency
   - NH₄⁺+ATP+HCO₃⁻ → Carbamoyl phosphate
   - Carbamoyl phosphate

3) OTC Deficiency
   - Ornithine
   - Ornithine

4a) Citrullinemia I
   - Arginosuccinate
   - Arginosuccinate

4b) Citrullinemia II
   - Aspartate
   - Aspartate

5) ASA
   - Arginine
   - Arginine

6) Arginase Def
   - Ornithine
   - Ornithine

7) HHH Syndrome
   - Citrulline
   - Citrulline

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Symptoms and Presentation

- Hyperammonemia

- Neurological symptoms
  - Seizures, lethargy, altered mental status

- Gastrointestinal symptoms
  - Vomiting, food avoidance, diarrhea, nausea

- Vomiting, Protein refusal

- Neonatal-Rapid deterioration
  - Respiratory alkalosis

- Infancy-Less acute

- Childhood and later-Chronic
Symptoms and Presentation II

• Specific disorders presentations
  o Arginase deficiency-episodic hyperammonemia. Spasticity
  o HHH-universal physical and mental developmental delay
  o Citrullinemia II-neuropsychiatric defects, cholestasis and other hepatic abnormalities

• Acute encephalopathic events can occur at all stages
Laboratory Tests

- **Chemistries**
  - Ammonia
  - Electrolytes and glucose
  - pH
  - BUN
  - Blood amino acids
  - Urine Organic Acids (Orotic acid)
  - Lactic acid
- **DNA testing**
- **Newborn screening**
Ammonia Testing

Variables that can affect interpretation

- Timing
- Arterial or venous sample
- Temperature
- Handling
- Different units
Example: OTC deficiency

**OTC Deficiency**

Aspartate → Arginosuccinate → Arginine → Urea

Glutamate → Citrulline

Citrulline → Ornithine → Arginase

NH₄⁺ + ATP + HCO₃⁻ → Carbamoyl phosphate → Orotic acid

N-Acetylglutamate Synthase

Carbamoyl-phosphate Synthase

Aspartate → Acetyl-CoA

N-Acetylglutamate

Citrin

ORNT1

Mitochondrion

Cytosol

Figure adapted with permission from Garg U, Smith LD, Heese BA, eds. Laboratory Diagnosis of Inherited Metabolic Diseases. Washington, DC: AACC; 2012:55–64. © AACC.
Example: Arginase deficiency

Aspartate → Arginosuccinate → Arginase Def → Argininosuccinate Lyase → Arginine → Urea

Citrulline → Ornithine → ORNT1 → Citrin

Glutamate → Aspartate → N-Acetylglutamate Synthase

Acetyl-CoA → Carbamoyl phosphate Synthase

NH₄⁺+ATP+HCO₃⁻ → Carbamoyl phosphate → Orotic acid
<table>
<thead>
<tr>
<th>Disorder</th>
<th>NH₄</th>
<th>BUN</th>
<th>Amino Acid Results</th>
<th>Organic Acid Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPS</td>
<td>↑-↑↑</td>
<td>↓</td>
<td>↓-N Arg, Citr, / ↑ Ala, Gln</td>
<td>↓ orotic</td>
</tr>
<tr>
<td>OTC</td>
<td>N-↑↑</td>
<td>↓</td>
<td>↑ Ala, Gln, Orn ↓ Arg ↓-N Citr</td>
<td>↑-↑↑ orotic</td>
</tr>
<tr>
<td>Citr I</td>
<td>↑↑</td>
<td>↓</td>
<td>↑↑↑ Citr(P/U)/ ↑ Ala, Gln ↓↓ Arg</td>
<td>↑-↑↑ orotic</td>
</tr>
<tr>
<td>Citr II</td>
<td>↑</td>
<td></td>
<td>↑ Gln,Citr N-↑ Arg</td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>↑-↑↑</td>
<td>↓</td>
<td>↑↑↑ ASA / Arg N-↑ Ala, Gln, Citr</td>
<td>↑↑ orotic</td>
</tr>
<tr>
<td>Arginase</td>
<td>N-↑↑</td>
<td>↓</td>
<td>↑↑↑ Arg</td>
<td>↑-↑↑ orotic</td>
</tr>
<tr>
<td>NAGS</td>
<td>↑-↑↑</td>
<td>↓</td>
<td>↓↓ Arg (P)/↓-N Citr/ ↑ Ala, Gln</td>
<td>↓ orotic</td>
</tr>
<tr>
<td>HHH</td>
<td>↑-↑↑</td>
<td></td>
<td>↑↑ Homocitrulline/↑ Orn, Gln (P),</td>
<td>↑ orotic</td>
</tr>
</tbody>
</table>

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Treatment

• Acute treatment
  1. Ammonia reduction
     – Administer nitrogen scavenger (Ammonul)
     – Hemodialysis
  2. Reverse catabolic state
     – Fluid management
     – Stop/restrict protein intake
     – IV L-arginine
  3. Reduce risk of neurologic damage
Treatment II

• Extended management
  o Nutritional control
  o Prophylaxis to viral infection
  o Disease specific treatments, including liver transplant
Summary

- The Urea Cycle is the metabolic pathway by which ammonia is detoxified and excreted as urea.
- Genetic defects in the enzymes that catalyze the urea cycle can result in the pathological accumulation of ammonia.
- Ammonia is the key test for suspicion of UCDs, be aware of testing pitfalls.
- Biochemical genetic tests can help identify the specific disorder and monitor treatment.
References


Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

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