Clinical presentations of late-onset urea cycle defects you should not miss

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American College of Medical Genetics and Genomics Satellite Symposium
Age is no barrier: time to consider late-onset urea cycle disorders

Salt Lake City, Utah
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COI

• I have been a consultant to Hyperion Therapeutics, Inc.

• I have received an honorarium from Recordati Rare Diseases

• I have been a local-site Principal Investigator of clinical trials sponsored by Hyperion Therapeutics, Inc.

• I have been a Data Safety Monitoring Board member for a clinical trial sponsored by Hyperion Therapeutics, Inc.
Key Points

• The neonatal presentation of urea cycle defects is that of progressive neurologic symptoms that may mimic a bowel obstruction (emesis) or sepsis (lethargy and poor feeding).

• Late-onset presentations (greater than one month of age) are multiple and are also non-specific.

• Failure to recognize these presentations results in delayed diagnoses, irreversible neurologic damage, and death.
Which of the following is false?

Individuals with urea cycle defects may first exhibit symptoms:

a) In the neonatal period - True
b) As toddlers - True
c) As school-age children - True
d) As teenagers - True
e) As young adults - True
f) In pregnancy - True
g) In their seventh decade - True
Which of the following is false?

Precipitants of hyperammonemia in individuals with late-onset urea cycle defects include:

a) A switch from formula to whole milk - True
b) A gastrointestinal illness - True
c) Valproate - True
d) Steroids - True
e) Delivery of a child - True
f) Gastrointestinal bleed - True
g) Total parenteral nutrition - True
Case Presentation

• 13 month old female with a two week history of a vomiting illness, now with irritability and lethargy

• She had emesis followed by sleepiness, had “looked past” her parents

• Symptoms had improved, then returned; she was sent to the emergency room by her doctor

• Recently she had switched from drinking formula to drinking whole milk
Case Presentation

• Ammonia was elevated at 198 µmol/L (RR < 57 µmol/L)

• Metabolic service contacted, ammonia was repeated, still close to 200 µmol/L
Case Presentation

• ED Treatment
  - 10% dextrose at 1.5 times maintenance
  - Sodium benzoate and sodium phenylbutyrate at 250 mg/kg in 10% dextrose over 90 minutes

• Urea cycle defect suspected
Case Presentation

• Metabolic laboratories ordered
  ▪ Plasma amino acids
  ▪ Urine organic acids
  ▪ Acylcarnitine profile
  ▪ Urine orotic acid - quantitative

• Samples walked to lab
  ▪ Plasma amino acids showed high glutamine and low citrulline
  ▪ Urine organic acids showed orotic acid and no other organic acids
  ▪ Acylcarnitine profile was normal
Case Presentation

• Metabolic laboratories ordered
  - Plasma amino acids
  - Urine organic acids
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  - Urine orotic acid - quantitative

• Samples walked to lab
  - Plasma amino acids showed high glutamine and low citrulline
  - Urine organic acids showed orotic acid and no other organic acids
  - Acylcarnitine profile was normal
  - Quantitative orotic acid value was markedly elevated
Female OTC Heterozygote

- Patient diagnosed with OTC deficiency, confirmed by deletion in OTC gene
- Mother is not a carrier, younger sister is unaffected
- Treated with an ammonia scavenging medication, citrulline, a low protein diet supplemented with essential amino acids
The Urea Cycle

- Urea
- NH₃ + CO₂ + 2 ATP + H₂O
- Aspartate
- Carbamyl Aspartate
- Dihydroorotate
Which of the following is false?

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d) Steroids - True
e) Delivery of a child - True
f) Gastrointestinal bleed - True
g) Total parenteral nutrition - True
Case Presentation

• 7 year old male with normal growth and development

• Had a vomiting illness that lasted 3 days with poor intake

• Became combative and told his mother he could not see

• Was brought to the Emergency Room, ammonia was over 300 \( \mu \text{mol/L} \)

• Was treated with IV dextrose and ammonia scavenger therapy
Male OTC Hemizygote

- Ammonia was normal within twelve hours

- He had altered mental status for several days

- Acute laboratories showed elevated glutamine, low citrulline, and elevated orotic acid

- These were normal when he was well

- OTC DNA gene sequencing did not identify a mutation
Which of the following is false?

Precipitants of hyperammonemia in individuals with late-onset urea cycle defects include:

a) A switch from formula to whole milk - True
b) A gastrointestinal illness - True
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d) Steroids - True
e) Delivery of a child - True
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g) Total parenteral nutrition - True
Case Presentation

• 12 year old male with a history of developmental delay and episodic ataxia, also with behavioral problems

• Developed valproate induced hyperammonemia: 244 μmol/L

• Metabolic service recommended plasma amino acids and urine organic acids

• Glutamine and citrulline were normal, orotic acid was elevated in organic acids
Male OTC Hemizygote

• OTC gene sequencing identified an A208T mutation

• He receives arginine therapy alone

• His brother has no history of ataxia, had a normal ammonia level, normal glutamine and citrulline and a two fold elevation of orotic acid on quantitative testing

• He also has the A208T mutation
Which of the following is false?

Precipitants of hyperammonemia in individuals with late-onset urea cycle defects include:

a) A switch from formula to whole milk - True
b) A gastrointestinal illness - True
c) Valproate - True
d) **Steroids** - True
e) Delivery of a child - True
f) Gastrointestinal bleed - True
g) Total parenteral nutrition - True
Case Presentation

• 50 year old man with no health concerns received steroids post sinus surgery

• He developed altered mental status

• When an ammonia level was checked it was over 600 μmol/L

• He was diagnosed with carbamoyl phosphate synthetase 1 deficiency
Which of the following is false?

Precipitants of hyperammonemia in individuals with late-onset urea cycle defects include:

a) A switch from formula to whole milk - True
b) A gastrointestinal illness - True
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d) Steroids - True
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f) Gastrointestinal bleed - True
g) Total parenteral nutrition - True
Case Presentation

• A 32 year old female developed altered mental status after delivering her first child

• An EEG indicated hepatic encephalopathy, and an ammonia level was elevated

• She had a history of developmental delay

• A brother had died in the newborn period

• She has a known pathogenic mutation in the OTC gene
Which of the following is false?

Precipitants of hyperammonemia in individuals with late-onset urea cycle defects include:

a) A switch from formula to whole milk  - True
b) A gastrointestinal illness  - True
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f) Gastrointestinal bleed  - True
g) Total parenteral nutrition  - True
Case Presentation

• A 15 month old previously healthy girl presented to the emergency room with progressive encephalopathy and a possible seizure, after a 10 day illness

• She had hepatomegaly, and hyperammonemia: 226 μmol/L

• AST and ALT were markedly elevated at 394 and 851 IU/L, respectively, INR was 4.4, PTT was normal

• Plasma amino acids showed elevated citrulline without argininosuccinate

• DNA and RNA analysis confirmed argininosuccinate synthase deficiency
Liver Failure in Citrullinemia Type 1

Ammonia - 225 µmol/L
INR - 6.6
ALT - 20,000 IU/L

Faghouiry et al. Mol Genet Metab. 2011 Apr 102 (4): 413-17
Case Presentation

• A 5 year old girl had a history of one seizure and brittle hair

• She was developmentally normal

• Her sister had an abnormal newborn screen and was diagnosed with argininosuccinate lyase deficiency

• She also has this condition and is now treated for this
Case Presentation

• An 18 year old male with intellectual disability and cerebral palsy was admitted for evaluation for liver transplant

• He had persistently elevated AST and ALT

• History revealed that he had walked well as a child but had developed lower leg spasticity in childhood

• Evaluation for liver failure included plasma amino acid analysis
Case Presentation

• Plasma amino acid analysis identified extremely elevated arginine

• He had mild hyperammononemia on non-fasting testing

• Enzyme activity in red blood cells confirmed arginase deficiency
The Urea Cycle

- Carbamoyl phosphate synthetase 1
- Ornithine transcarbamylase
- Argininosuccinate synthase
- Argininosuccinate lyase
- Arginase

Atlas of Inherited Metabolic Diseases. Nyhan, Barshop, Ozand, Editors
Case Presentation

• 32 month old female seen in GI clinic for intermittent vomiting, since switching from formula to whole milk

• Physical examination was normal, testing for malrotation of the gut was normal

• Other testing: *Helicobacter pylori*, sedimentation rate, celiac screen, liver and kidney function, lipase, thyroid, food allergy panel, stool hemocult, abdominal X-ray and ultrasound

• Started on Prevacid for presumed reflux, given fortified rice milk, planned follow-up in three weeks
Case Presentation

• Radiographic studies: borderline hepatomegaly

• Laboratory studies: AST 80 and ALT 257 IU/L - elevated

• Plan: Repeat hepatic function panel in two weeks, get viral, rheumatologic, alpha-1 antitrypsin, anti-smooth muscle antibodies and anti-liver, kidney and muscle antibody

• Repeat AST and ALT: 60, 130 IU/L, bilirubin normal

• Impression: Isolated idiopathic hepatitis
Case Presentation

• Plan: recheck AST/ALT in 6 months and obtain urine organic acids, plasma amino acids, acylcarnitine profile, lactate and ammonia

• Ammonia was elevated at 300 μmol/L

• She was referred to the emergency room

• OTC was identified biochemically and via DNA, R23X mutation in the OTC gene
Female with liver failure diagnosed with OTCD - UCLA
Male with OTCD in a hyperammonemic event - Colorado
Acute Liver Failure

- Is not well described in urea cycle defects
- Has been reported in isolated case reports
- Urea cycle defects may not be included in the differential diagnosis of acute liver failure
Pediatric Acute Liver Failure

- Liver based coagulopathy (not corrected by Vitamin K) with
  - INR $\geq 1.5$ or PT $\geq 15$ in the presence of encephalopathy, or
  - INR $\geq 2$ or PT $\geq 20$ in the absence of encephalopathy

- Severe hepatic dysfunction occurring within eight weeks of onset of illness

- No known chronic liver disease
Definitions for this Study

• Liver failure (no Vitamin K criteria)
  - INR ≥ 2.0 or PT ≥ 20 seconds

• Liver dysfunction
  - INR ≥ 1.5 and < 2.0, or PT ≥ 15 seconds and < 20 seconds

• Hepatocellular injury
  - AST or ALT ≥ 250 units/liter
Female with liver failure diagnosed with OTCD - UCLA
# Results

## Liver Laboratory Values in 71 Individuals with OTCD

<table>
<thead>
<tr>
<th>Clinical Classification (n)</th>
<th>Ammonia µmol/L</th>
<th>ALT IU/L</th>
<th>AST IU/L</th>
<th>PT seconds</th>
<th>INR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
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<tr>
<td>Neonatal Male (12)</td>
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<td>22-256</td>
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<td>Severe (9)</td>
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<td>923</td>
<td>16-2089</td>
<td>1063</td>
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<tr>
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<td>37.6-332</td>
<td>331</td>
<td>13-1223</td>
<td>137</td>
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<tr>
<td>Mild (15)*</td>
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<td>9.2-297</td>
<td>102</td>
<td>10-689</td>
<td>71.1</td>
</tr>
<tr>
<td>Asymptomatic (22)</td>
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<td>9-104.5</td>
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Acute Liver Failure, Liver Dysfunction, and Hepatocellular Injury in Symptomatic and Asymptomatic Individuals with OTCD

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<tr>
<th>Clinical Classification (N)</th>
<th>Acute Liver Failure</th>
<th>Liver Dysfunction</th>
<th>Hepatocellular Injury Only</th>
<th>No Known Liver Lab Abnormality</th>
<th>Percent with either ALF/LD/HCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal Male (12)</td>
<td>58%</td>
<td>17%</td>
<td>0%</td>
<td>25%</td>
<td>75% (9/12)</td>
</tr>
<tr>
<td>Severe (9)</td>
<td>56%</td>
<td>11%</td>
<td>0%</td>
<td>33%</td>
<td>67% (6/9)</td>
</tr>
<tr>
<td>Moderate (12)</td>
<td>17%</td>
<td>25%</td>
<td>8%</td>
<td>50%</td>
<td>50% (6/12)</td>
</tr>
<tr>
<td>Mild (16)</td>
<td>0%</td>
<td>25%</td>
<td>19%</td>
<td>56%</td>
<td>44% (7/16)</td>
</tr>
<tr>
<td>Asymptomatic (22)</td>
<td>0%</td>
<td>9%</td>
<td>0%</td>
<td>91%</td>
<td>9% (2/22)</td>
</tr>
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</table>
3 month old OTCD female: ballooning hepatocytes, multi-nucleated cells
Conclusions

• Greater than half of symptomatic individuals with OTCD had liver lab abnormalities at least once

• This was recurrent in some

• This is an under-recognized feature of ornithine transcarbamylase deficiency
THE UREA CYCLE

N-Acetylglutamate Synthase
Carbamyl Phosphate Synthase
Ornithine Transcarbamylase
(Proximal Disorders)

THE UREA CYCLE

Argininosuccinate Lyase

Argininosuccinate Synthase

Arginase

(Distal Disorders)

Citrullinemia Type 2:
- ↑ NH3
- ↑ Citrulline
  - Neonatal Intrahepatic Cholestasis
  - Adult-Onset Citrullinemia type 2

H-H-H-H Syndrome:
- ↑ NH3
- ↑ Ornithine
Homocitrullinuria

Which of the following is false?

Signs and symptoms of elevated ammonia include:

a) Sleepiness
b) Irritability
c) Hallucinations
d) Seizures
e) Headache
f) Vomiting
g) Loss of vision
h) Combative behavior
i) Ataxia
Which of the following is **false**?

Signs and symptoms of elevated ammonia include:

a) Sleepiness  
b) Irritability  
c) Hallucinations  
d) Seizures  
e) Headache  
f) Vomiting  
g) Loss of vision  
h) Combative behavior  
i) Ataxia

None is false
Which of the following is false?

Expected laboratory findings in urea cycle defects include:

a) Elevated ammonia
b) Normal or low urinary ketones
c) Increased blood pH
d) Elevated INR and Prothrombin time (PT)
e) Elevated AST and ALT
f) Elevated Partial thromboplastin time (PTT)
g) Decreased BUN
h) Low serum sodium
Which of the following is false?

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Thank you to:

• UCLA
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  ▪ Stephen Cederbaum, MD
  ▪ Nagmeh Dorrani

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  ▪ Mendel Tuchman, MD
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  ▪ Jennifer Seminara, MPH
  ▪ The UCDC PIs, study coordinators, and study subjects

• University of Colorado
  ▪ Gastroenterology, Hepatology and Nutrition
    ▪ Ronald Sokol, MD

• Clinical Genetics and Metabolism
  ▪ Curtis Coughlin II, CGC, MBE
    Study Coordinator, now co-PI
  ▪ Shannon Scrivner, CGC
    Study Coordinator
  ▪ Kim Showers, GC Student
  ▪ Anna Essendrup, GC Student
Case Presentations

• Female OTC - diet change with increased protein
• Late-onset OTC male - illness and catabolism
• Late-onset OTC male “unmasked” by valproate
• Late-onset CPS1 “unmasked” by steroids
• Late-onset NAGS deficiency - trauma
• Late-onset female OTC - post-partum
• Late-onset female citrullinemia type 1 - illness
• Late-onset argininosuccinate lysase deficiency – seizures and brittle hair
• Late-onset arginase deficiency – spasticity and liver failure
• Late-onset OTC – recurrent emesis and “hepatitis”