Urea Cycle Disorders and Hyperammonemia:

Diagnosable

Treatable

Screenable

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Disclosure

• Grant/Research Support: NIH RDCRN
Frequencies in U.S., Europe, and China (LSD lower in China)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKU</td>
<td>1:15,000, 1:8000 China</td>
</tr>
<tr>
<td>MSUD</td>
<td>1:75,000</td>
</tr>
<tr>
<td>Galactosemia</td>
<td><strong>1:40,000</strong></td>
</tr>
<tr>
<td>MCAD</td>
<td>1:15,000</td>
</tr>
<tr>
<td>MMA</td>
<td>1:20,000</td>
</tr>
<tr>
<td>PA</td>
<td>1:50,000</td>
</tr>
<tr>
<td>Urea Cycle</td>
<td>1:33,000 to &lt; 1:100,000</td>
</tr>
<tr>
<td>Gaucher’s</td>
<td>1:60,000</td>
</tr>
<tr>
<td>Fabry’s</td>
<td>1:80,000</td>
</tr>
<tr>
<td>Hurler’s</td>
<td>&gt; 1:100,000</td>
</tr>
</tbody>
</table>
Why we will cover it:

Metabolic disease or inborn errors of metabolism represent one of the few genetic diseases where prompt recognition and treatment can significantly improve outcome and morbidity/mortality particularly in intermediary metabolism.
Urea cycle disorders

- Essential pathway for nitrogen disposal
  - Converts N (ammonia and aspartate) to urea
  - Also generates arginine
  - Replenishes intermediates
- Entire cycle is present in the liver
  - No net gain or loss of intermediates in the liver
- Proximal cycle (NAGS, CPS, OTC) present in the gut
- Distal cycle (ASS, ASL, ARG) present in the kidney
The Classic Urea Cycle

HCO₃⁻ + NH₄⁺ + 2 ATP

- **CPSI**: Carbamyl Phosphate
- **OTC**: Ornithine Transcarbamoylase
- **ARG**: Arginase
- **ASS**: Argininosuccinate Synthase
- **ASL**: Argininosuccinate Lyase

**Mitochondria**

**Cytoplasm**

- **N-acetylglutamate**
- **Citrulline**
- **Aspartate**
- **Arginosuccinate**
- **Fumarate**

Hans Krebs
Described it in 1923
The Enzymes of the Cycle Don’t Just Process Ammonia to Urea

Liver

Bulk nitrogen to urea
Little citrulline excreted
Little arginine excreted
Nitric oxide small amt

Division of Genetics & Metabolism
INTESTINE: AMMONIA PROCESSING TO ARGinine & CITRULLINE

Intestine

Bulk nitrogen to arginine and citrulline for export

Nitric oxide small amt
Heart and Lung
Take circulating citrulline and internal arginine to make nitric oxide
Sources of Urea Cycle Disorder Outcome Data

RETROSPECTIVE:

U.S.A. Data
Summar et al (Acta Ped, 2008): Data for Phenylacetate/Benzoate therapy for acute hyperammonemia collected between 1982-2003. 260 patients enrolled with 975 episodes of hyperammonemia. 88 were newborn onset (first 30 days)

French Data
Nassogne et al (JIMD, 2005) From Necker-Enfants Malades Hospital. Outcome data on 217 patients collected by Nassogne et al. These included 121 neonatal onset and 96 late onset.

Japanese Data

PROSPECTIVE:

NIH UCDC Data
580+ patients with a molecular diagnosis of a urea cycle disorder enrolled in a national longitudinal study of outcomes. The Urea Cycle Disorders Consortium is in year 7 (10 funded). Currently 15 active academic sites. Many asymptomatic carrier OTC females
Things that Disrupt the Urea Cycle

- Rare genetic defects in a urea cycle enzyme
- Damage to the liver and gut
  - Viral
  - Chemical (ETOH or other)
  - Hypoxia, shock
  - Cardiopulmonary bypass
  - Metabolic (galactosemia, tyrosinemia, Wilson’s dz, etc.)
- Vascular Bypass of the liver by cirrhosis or vascular damage
- Drug and Molecule effects
  - Valproic acid
  - Chemotherapy (cyclophosphamide primarily)
  - Organic acids (propionic, methylmalonic, isovaleric
- Mild Genetic Changes in the Cycle Combined with the above.
The Classic Symptoms

- Encephalopathy and Cerebral Edema
- Hyperventilation in early stages
- Floppy
- Vomiting (typically older children)
- Neurologic posturing
- Low body temperature
- Respiratory alkalosis (transient)
Presenting Symptoms in 260 patients at first hyperammonemia

- **Neurologic symptoms (100%)**
  - Decreased level of consciousness (63%)
  - Abnormal motor function or tone (30%)
  - Seizures (10%)

- **Vomiting (19%)**

- **Infection (30%)**

- **Subjective: Decreased appetite, fussy**

- **Physiologic: Respiratory alkalosis (secondary to cerebral edema) followed by apnea**
Ammonia CNS Toxicity

- **Direct Effects**
  - Swelling
  - Effects excitatory and inhibitory post-synaptic potentials
  - Effects expression of glutamate transporter
  - Effects peripheral-type benzodiazepine receptors expression (neurosteroids)
  - Inhibits alpha-ketoglutarate dehydrogenase

- **Indirect Effects**
  - Increased glutamine from glutamate results in edema
  - Increased glutamine increases transport of aromatic amino acids increasing tryptophan which converts to serotonin.
Prevalence of Epilepsy

• Prevalence of epilepsy in patients with urea cycle disorders is unknown

• Data from a multicenter study of UCDs as part of a Urea Cycle Disorders Consortium (UCDC) suggest that 9.6% of patients with a urea cycle disorder present with seizures
  – 4.8% experiencing subsequent episodes
  – half of enrolled patients had an abnormal neurological exam, raising concern that this population is at increased risk for seizure
60% of patients outside immediate newborn period

Triggers for Adult Onset Disease Assuming Partial Enzyme Deficiency

- Valproic acid (5 published reports)
- Post-partum stress (1 report)
- Heart Lung Transplant
- Short bowel and kidney disease
- Parenteral nutrition
- GI bleeding

Excessive Hyperammonemia is also reported in
- Chemotherapy
- Severe hepatic disease
Other Metabolic Dz  
Neurologic Dz  
Sepsis

Hyperammonemia  
> 100 umol/l, ± low BUN

Evidence for Severe Hepatic Dysfunction

Draw Amino Acids and Organic Acids  
Repeat ammonia

Normal Ammonia

Newborn Lethargy

Hepatitis (infection, etc)  
Tyrosinemia, galactosemia  
Organic Acidemia  
Chemical  
Structural  
Sepsis

Workup and Treat For Possible Sepsis

Initiate Treatment for Possible Urea Cycle Defect

▲ Glycine  
▲ BCAAs  
▲ Ketones  
▲ Lactate

Yes  
No (yes for some UCDS)  
Yes  
Yes

> 100 umol/l, ± low BUN  
Evidence for Severe Hepatic Dysfunction  
Normal Ammonia  
No

Diagnostic Flow Chart for Acute Hyperammonemia
Diagnostic Flow Chart for Acute Hyperammonemia

- Newborn Lethargy
  - Yes
  - Hyperammonemia > 100 umol/l, ± low BUN
    - Yes
      - Evidence for Severe Hepatic Dysfunction
        - Yes
          - Initiate Treatment for Possible Urea Cycle Defect
    - No (yes for some UCDS)
      - No

- Normal Ammonia
  - Draw Amino Acids and Organic Acids
    - Repeat ammonia
      - ▼Citrulline
        - ▼Oratate ▲
          - CPSID: carbamyl phosphate synthetase I deficiency
          - NAGSD: n-acetylglutamate synthase deficiency
          - OTCD: ornithine transcarbamylase deficiency
          - ASSD: argininosuccinic acid synthase deficiency
          - CitD: citrin deficiency (citrullinemia type II)
          - ASLD: argininosuccinic acid lyase deficiency
          - ArgD: arginase deficiency
          - HHH: homocitrullinuria, hyperornithinemia, hyperammonemia

- Hyperammonemia > 100 umol/l, ± low BUN
  - Yes
    - Evidence for Severe Hepatic Dysfunction
      - Yes
        - Initiate Treatment for Possible Urea Cycle Defect
      - No
        - Yes
          - Hepatitis (infection, etc)
            - Tyrosinemia, galactosemia
            - Organic Acidemia
            - Chemical
            - Structural
            - Sepsis

- Hepatitis (infection, etc)
  - Tyrosinemia, galactosemia
    - Organic Acidemia
      - Chemical
        - Structural
          - Sepsis

- Hepatitis (infection, etc)
  - Tyrosinemia, galactosemia
  - Organic Acidemia
  - Chemical
  - Structural
  - Sepsis
Outcomes: Then and Now

Data from the UCDC
Outcome Data in Early Series: Batshaw and Brusilow
UCD Patients by Diagnosis
Data current as of July 2, 2012
UCD Subjects By Onset

Data current as of July 2, 2012

- OTCD
- ALD
- ASD
- CPSID
- Dx Pending
- ARGD
- CITRD
- HHH/ORNTD
- NAGS

Legend:
- Neonatal Onset (N=150)
- Late Onset (N=421)
# Weight and Height (%, Z-score mean) by CDC Growth Standards *

<table>
<thead>
<tr>
<th></th>
<th>0 – 6 mos</th>
<th>6 -12 mos</th>
<th>1 – 3 yrs</th>
<th>3 – 10 yrs</th>
<th>10 – 18 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt, Z-score</td>
<td>-0.22</td>
<td>-0.10</td>
<td>-0.40</td>
<td>-0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>Wt, %</td>
<td>45</td>
<td>49</td>
<td>42</td>
<td>49</td>
<td>52</td>
</tr>
<tr>
<td>Height, Z-score</td>
<td>-1.2</td>
<td>-0.80</td>
<td>-0.44</td>
<td>-0.6</td>
<td>-0.66</td>
</tr>
<tr>
<td>Height, %</td>
<td>39</td>
<td>46</td>
<td>42</td>
<td>35</td>
<td>35</td>
</tr>
</tbody>
</table>

* 2000 CDC Growth Charts for the U.S. Center for Disease Control and Prevention National Center for Health Statistics
http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm
# Children 2-18 yrs

## Weight Status Category Percentile Distribution by BMI % *

<table>
<thead>
<tr>
<th>Age Interval</th>
<th>Underweight BMI &lt;= 5%</th>
<th>Normal BMI 5 – 85%</th>
<th>Overweight BMI &gt;85 &lt;=95%</th>
<th>Obese &gt;=95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 – 5 years</td>
<td>3</td>
<td>77</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>5 – 10 years</td>
<td>3</td>
<td>70</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>10 – 18 years</td>
<td>3</td>
<td>72</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

* Center for Disease Control and Prevention
Healthy Weight Assessment for Children
http://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html
## NEUROPSYCHOLOGICAL AND BEHAVIORAL OUTCOMES FOR INFANTS

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>DQ</th>
<th>Language Delay</th>
<th>Motor Delay</th>
<th>ABAS-II GAC &lt; 85</th>
<th>Sleep Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTC n=20</td>
<td>83</td>
<td>56%</td>
<td>55%</td>
<td>50%</td>
<td>24%</td>
</tr>
<tr>
<td>ASD n=17 Citrullinemia</td>
<td>92</td>
<td>25%</td>
<td>29%</td>
<td>33%</td>
<td>15%</td>
</tr>
<tr>
<td>ALD n=19 ASA</td>
<td>85</td>
<td>52%</td>
<td>47%</td>
<td>44%</td>
<td>16%</td>
</tr>
<tr>
<td>CPS (n=3)</td>
<td>83</td>
<td>0</td>
<td>67%</td>
<td>33%</td>
<td>0</td>
</tr>
</tbody>
</table>
## Neuropsychological and Behavioral Outcomes for School Age Disorder

<table>
<thead>
<tr>
<th>DISORDER (n)</th>
<th>Full Scale IQ</th>
<th>Verbal IQ</th>
<th>Performance IQ</th>
<th>ABAS-II GAC &lt; 85</th>
<th>BRIEF GEC =&gt;65</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTC n=75</td>
<td>97</td>
<td>99</td>
<td>93</td>
<td>28%</td>
<td>65%</td>
</tr>
<tr>
<td>ASD n=23</td>
<td>88</td>
<td>92</td>
<td>87</td>
<td>16%</td>
<td>61%</td>
</tr>
<tr>
<td>(Citrullinemia)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALD n=24</td>
<td>73</td>
<td>78</td>
<td>73</td>
<td>21%</td>
<td>79%</td>
</tr>
<tr>
<td>(ASA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPS n=2</td>
<td>87,91</td>
<td>88,100</td>
<td>82,97</td>
<td>100%</td>
<td>0</td>
</tr>
</tbody>
</table>

- **OTC** (n=75)
- **ASD** (Citrullinemia) (n=23)
- **ALD** (ASA) (n=24)
- **CPS** (n=2)
A third child with CPS is in the study and in special classes but no neuropsychological evaluations were done.
<table>
<thead>
<tr>
<th>DISORDER</th>
<th>Full Scale IQ</th>
<th>Verbal IQ</th>
<th>Performance IQ</th>
<th>ABAS-II GAC &lt;85</th>
<th>BRIEF GEC =&gt;65</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTC n=124</td>
<td>101</td>
<td>101</td>
<td>99</td>
<td>40%</td>
<td>90%</td>
</tr>
<tr>
<td>ASD n=7</td>
<td>61</td>
<td>66</td>
<td>62</td>
<td>60%</td>
<td>100%</td>
</tr>
<tr>
<td>(citrullinemia)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALD n=13</td>
<td>64</td>
<td>66</td>
<td>67</td>
<td>56%</td>
<td>67%</td>
</tr>
<tr>
<td>(ASA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPS n=2</td>
<td>62,86</td>
<td>71,87</td>
<td>58,88</td>
<td>100%</td>
<td>--</td>
</tr>
</tbody>
</table>
Possible Age or Year of Diagnosis Effects-
Neonatal group

- First Consensus Meeting
- Formation of Consortium
T1 Weighted FLAIR image in a female with partial OTCD showing abnormal white matter signal in the deep white matter of the centrum semiovale and motor association cortex. Such white matter findings may be reversible and are felt to be markers of recent hyperammonemia. There is also cortical atrophy with widened sulci. (courtesy of Dr. Andrea Gropman, CNMC, Washington, D.C.)

DTI tractography showing blunting of fibers in patient with partial OTCD (bottom) as compared to control.