Ornithine Transcarbamylase Deficiency

Newborn Screening TAC Meeting

Angela Sun, MD, FACMG
Associate Professor, Department of Pediatrics
University of Washington School of Medicine
Seattle Children’s Hospital
OTC Deficiency

• Urea cycle – the body’s way of eliminating waste nitrogen
• Ammonia is produced from protein breakdown
• Incidence 1/17,000 in U.S.
• X-linked

Hyperammonemia

• Cerebral edema

• Triggers
  • Birth
  • Infection (flu, stomach virus, common cold)
  • Fever
  • Fasting
  • Medications (high dose steroids, valproic acid, L-asparaginase, etc.)
  • High protein load
  • Prolonged or intense exercise
OTC Clinical Presentation

• Neonatal (30%) – poor feeding, vomiting, lethargy, hyperventilation, seizures, coma, death
  • Mortality 74-90%

• Childhood (60%) – poor growth, developmental delay, hypotonia, episodic encephalopathy with ataxia, seizures

• Adolescent/adult (10%) – chronic neurological or psychiatric symptoms, behavioral problems, migraines, episodes of disorientation or psychosis triggered by high protein intake or stress, protein aversion

### Table 1 Epidemiological characteristics of the patients

<table>
<thead>
<tr>
<th></th>
<th>Neonates</th>
<th>Group 1 m-16y</th>
<th>Group &gt;16y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>27</td>
<td>52</td>
<td>11</td>
</tr>
<tr>
<td>Males</td>
<td>22</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>females</td>
<td>5</td>
<td>31</td>
<td>6</td>
</tr>
<tr>
<td>Number of deceased at diagnosis</td>
<td>20</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>during follow up</td>
<td>13</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Number of decompensations per patient (and relative to mean length of follow-up)*</td>
<td>6,2 (1.0/yr)</td>
<td>2,5 (1/10 yrs)</td>
<td>1,4 (&lt;1/20 yrs)</td>
</tr>
<tr>
<td>Neurological score (IQ) at last follow up, N &gt; 80</td>
<td>90</td>
<td>92</td>
<td>Normal socio-professional insertion</td>
</tr>
<tr>
<td>Mean peak plasma ammonia at diagnosis (µmol/L), N &lt; 50 µmol/L</td>
<td>960</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>Mean plasma glutamine at diagnosis (µmol/L), N: 530 +/- 81 µmol/L</td>
<td>4110</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>Plasma citrulline at diagnosis (µmol/L), N: 26+/8 µmol/L</td>
<td>5</td>
<td>15</td>
<td>14</td>
</tr>
</tbody>
</table>

*Only the patients that survived beyond neonatal life were included.
Figure 1 Survival of OTCD patients by age of onset. Comparison of survival between the 1 mth-16 y and neonatal group. In the 1 mth-16 y group, the “critical” period (risk of death) is that between the first severe symptoms and diagnosis. In the neonatal form, there are two high-risk age intervals: the first days of life and the period between 1 and 7 years of age.
OTC Deficiency

- Survival
  - 9% if ammonia >1000
  - 90% if ammonia <500
- Children treated from birth (prenatal diagnosis) have better outcome as management of the first crisis is crucial
- In adults, death may occur during the first episode of decompensation if diagnosis unknown

Management

• Protein restriction
  • Based on age
  • Intact protein and essential amino acids

• Nitrogen scavengers
  • Sodium benzoate, sodium phenylbutyrate
  • Glycerol phenylbutyrate (Ravicti)
  • Ammonul (IV)

• Replenish urea cycle intermediates – arginine or citrulline

• For emergencies
  • Caloric support – high dextrose IV fluids, lipids
  • Hemodialysis

• Other – G-tube, early intervention services
Liver Transplantation

• Corrects the metabolic defect
• Generally performed by 6 months in severe form
• Allows liberalization of diet
• Neurocognitive deficits remain
• Long-term immunosuppression, monitoring labs
• 90% survival at 5 years