Long-term outcome of urea cycle disorders: report from a nationwide study in Japan

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Abstract:
Urea cycle disorders (UCDs) are inherited metabolic disorders with impaired nitrogen detoxification caused by defects of urea cycle enzymes. Patients with UCDs frequently present with hyperammonemic attacks leading to significant morbidity or death.

We conducted a nationwide questionnaire-based study between January 2000 and March 2018 to document all UCDs in Japan, including diagnoses, treatments, and outcomes. A total of 229 patients with UCDs were included in this study: 73 males and 53 females with ornithine transcarbamylase deficiency (OTCD), 33 patients with carbamoylphosphate synthetase 1 deficiency, 48 with argininosuccinate synthetase deficiency, 14 with argininosuccinate lyase deficiency, and 8 with arginase deficiency. Survival rates at 20 years of age of male and female patients with late-onset OTCD were 100% and 97.7%, respectively. Peak blood ammonia levels and onset time had a significant impact on the neurodevelopmental outcome (P<0.001 and P=0.028, respectively). Hemodialysis and liver transplantation did not prevent poor neurodevelopmental outcomes. While treatment including medication, hemodialysis, and liver transplantation may aid in decreasing blood ammonia and/or preventing severe hyperammonemia, a peak blood ammonia level ≥ 360 µmol/L was found to be a significant indicator for a poor neurodevelopmental outcome.

In conclusion, although current therapy for UCDs has advanced and helped saving lives, patients with peak blood ammonia levels ≥ 360 µmol/L at onset often have impaired neurodevelopmental outcomes. Therefore, novel neuroprotective measures should be developed to acquire better neurodevelopmental outcomes in these patients.
Table 1. Diagnosis and time of onset in patients with UCDs

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Time of onset</th>
<th>Enzyme deficiency (%)</th>
<th>Identifiable mutation (%)</th>
<th>Neonatal onset</th>
<th>Late onset</th>
<th>Prenatal Diagnosis</th>
<th>Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male OTCD (Median: 16 years 2 months, [IQR: 10 years 3 months – 28 years 10 months])</td>
<td></td>
<td>19 (26%)</td>
<td>48 (66%)</td>
<td>31 (42%)</td>
<td>34 (47%)</td>
<td>8 (11%)</td>
<td>0</td>
<td>73 (32%)</td>
</tr>
<tr>
<td>Female OTCD (Median: 11 years 4 months, [IQR: 5 years – 19 years 1 months])</td>
<td></td>
<td>15 (28%)</td>
<td>31 (58%)</td>
<td>3 (6%)</td>
<td>49 (92%)</td>
<td>0</td>
<td>1 (2%)</td>
<td>53 (23%)</td>
</tr>
<tr>
<td>CPSD (M:11, F:22) (Median: 9 years 4 months, [IQR: 5 years – 15 years 7 months])</td>
<td></td>
<td>4 (12%)</td>
<td>19 (58%)</td>
<td>27 (82%)</td>
<td>5 (15%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>33 (14%)</td>
</tr>
<tr>
<td>ASSD (M:22, F:26) (Median: 11 years 4 months, [IQR: 5 years 5 months – 17 years 3 months])</td>
<td></td>
<td>4 (8%)</td>
<td>22 (46%)</td>
<td>34 (71%)</td>
<td>9 (19%)</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
<td>48 (21%)</td>
</tr>
<tr>
<td>ASLD (M:9, F:5) (Median: 23 years 4 months, [IQR: 13 years 10 months – 30 years 3 months])</td>
<td></td>
<td>5 (36%)</td>
<td>8 (57%)</td>
<td>11 (79%)</td>
<td>3 (21%)</td>
<td>0</td>
<td>0</td>
<td>14 (6%)</td>
</tr>
<tr>
<td>ARGD (M:4, F:4) (Median: 21 years 8 months, [IQR: 15 years 6 months – 37 years 6 months])</td>
<td></td>
<td>6 (75%)</td>
<td>5 (63%)</td>
<td>2 (25%)</td>
<td>6 (75%)</td>
<td>0</td>
<td>0</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Total (M:119, F:110)</td>
<td></td>
<td>53 (23%)</td>
<td>133 (58%)</td>
<td>108 (47%)</td>
<td>106 (46%)</td>
<td>12 (5.2%)</td>
<td>3 (1.3%)</td>
<td>229 (100%)</td>
</tr>
</tbody>
</table>

DNA analysis was performed in 95 patients with OTCD (62 males, 33 females), 25 patients with CPSD, 62 patients with ASSD, 8 patients with ASLD and 6 patients with ARGD.

In the analyzed patients, identifiable mutations were detected in 77% (48/62) of male-OTCD, 94% (31/33) of female-OTCD, 88% (22/25) of CPSD, 85% (22/26) of ASSD, 100% (8/8) of ASLD, and 83% (5/6) of ARGD.

One hundred eight patients (47%) developed symptoms in the neonatal period and 106 (46%) had symptoms after day 28 postpartum (late-onset). In the CPSD, ASSD, ASLD, and ARGD groups, 82% (27/33), 71% (34/48), 79% (11/14), and 25% (2/8), respectively, developed symptoms at the neonatal period.

Neonatal onset <28 days from birth; late-onset ≥28 days after birth.

Figure 1. Long-term outcome in UCDs in different studies

A. Survival curve in male patients with late-onset OTCD.
One male patient with OTCD developed symptoms at the age of 6 years and died with hyperammonemic attack at the age of 21 years (this study).

B. Survival curve in female patients with late-onset OTCD in different studies.
One female patient with onset at 8 years of age died during a hyperammonemic attack with cerebral hemorrhage (this study).

C. Survival curve in patients with neonatal onset UCDs in the present study.
For male and female OTCD patients in this study, the survival outcomes were improved compared to the previous cohorts. Survival rates of male patients with neonatal onset OTCD and de patients with neonatal onset CPSD, ASSD, and ASLD at age 20 years were 85.6% (N=32), 83.6% (N=28), 97.1% (N=35), and 78.8% (N=10), respectively. The long-term survival rate in neonatal onset male OTCD, CPSD, ASSD, and ASLD was expected to be improved in this study.
Figure 2. Neurodevelopmental outcome in UCDs depending on blood ammonia levels at onset.

A. Total cohort (N= 213, Hemodialysis group: N=129, Non-hemodialysis group: N=84).
B. Patients with neonatal onset OTCD (Total: N=33, Hemodialysis group: N=26, Non-hemodialysis group: N=7).
C. Patients with late-onset OTCD (Total: N=82, Hemodialysis group: N=18, Non-hemodialysis group: N=64).
D. Patients with CPSD (Total: N=32, Hemodialysis group: N=23, Non-hemodialysis group: N=9).
E. Patients with ASSD (Total: N=42, Hemodialysis group: N=13, Non-hemodialysis group: N=29).
F. Patients with ASLD (Total: N=13, Hemodialysis group: N=4, Non-hemodialysis group: N=9).
G. Patients with ARGD (Total: N=7).

A blood ammonia level greater than 360 µmol/L is an adverse marker for neurodevelopmental outcomes; only 19% (17/90) of UCD patients with blood ammonia levels exceeding 360 µmol/L acquired normal neurodevelopmental outcomes.

In neonatal onset OTCD, the maximum blood ammonia levels were 688 µmol/L (IQR: 335-1394), and 79% (26/33) received hemodialysis; 76% (25/33) developed mental handicaps or died. In late-onset OTCD (N=82), the maximum blood ammonia levels were a median of 235 µmol/L (IQR: 151-339), and 22% (18/82) received hemodialysis; 74% (61/82) had normal neurodevelopmental outcomes.

In conclusion, we reinvestigated the status, treatments, and long-term outcomes of UCDs in Japan. Even at present, when treatments such as medication, hemodialysis, and LT dramatically decrease blood ammonia and/or prevent severe hyperammonemia, a blood ammonia level ≥ 360 µmol/L is a significant adverse marker of the neurodevelopmental outcome. Novel and better neuroprotective measures are still needed for patients with hyperammonemia of ≥ 360 µmol/L to improve their neurodevelopmental outcome.