Introduction to the primary hyperoxalurias
Causes, Symptoms & Treatments

Prof. Dr. Bernd Hoppe
Hyperoxaluria

Underestimated as risk factor for calcium containing stones

Most frequent risk factor in our outpatient clinic

Often accompanied by hypocitraturia
Secondary hyperoxaluria

**Intestinum**
- Dietary intake: ~130 mg/d
  - >200 mg/d
- Bacterial degrading: 70-100 mg/d
- No degrading: 10-50 mg/d

**Oxalate pool**
- Feces: 10-50 mg/d
- PH I & II:
  - Normal: 20-45 mg/d (<0.5 mmol/d)
  - Secondary HyOx: 45-90 mg/d (0.5-1.0 mmol/1.73m²/d)
  - PH: >100 mg/d (>1.0 mmol/1.73m²/d)

**Urine**
- 15-45 mg/d
- >100 mg/d
<table>
<thead>
<tr>
<th>PH</th>
<th>Total No</th>
<th>Complete information genotype + outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH1</td>
<td>501</td>
<td>408</td>
</tr>
<tr>
<td>Male/female</td>
<td>284/215</td>
<td></td>
</tr>
<tr>
<td>No data</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>PH2</td>
<td>53</td>
<td>24</td>
</tr>
<tr>
<td>Male/female</td>
<td>19/31</td>
<td></td>
</tr>
<tr>
<td>No data</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>PH non1 – non2*</td>
<td>16</td>
<td>* Possibly type III PH</td>
</tr>
</tbody>
</table>
Note: Some patients may have been sent from other countries for diagnosis only
Primary Hyperoxaluria Type I

Autosomal-recessive inherited defect of the glycolate metabolism

Defect of liver specific peroxisomal Alanine-Glyoxylate Aminotransferase (AGT, 2q37.3)

Prevalence: 1.2-2/10^6
Characteristics

Extremely elevated urinary excretion of both oxalate and glycolate (> 1 mmol/1.73m²/24h)

Urinary calcium-oxalate supersaturation

Recurrent Urolithiasis, progressive nephrocalcinosis, systemic oxalosis, early end stage renal failure
Nephrocalcinosis
Systemic oxalosis: bone
Systemic oxalosis: bone marrow/renal

Cause of treatment resistant anemia
Systemic oxalosis: skin
Systemic oxalosis: retina
Clinical heterogeneity

Follow up
- Infantile form, early end stage renal failure
- Adult form, first symptoms later in life

Genotype/Phenotype correlation?
- intrafamiliar differences
- Prenatal diagnosis possible

Recommendation?
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>KJ age (yrs)</th>
<th>11.9</th>
<th>12.9</th>
<th>13.1</th>
<th>14.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>creat (mg/dl)</td>
<td>1.38</td>
<td>2.36</td>
<td>2.78</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>Uox (mmol/d)</td>
<td>3.65</td>
<td>3.1</td>
<td>2.2</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>NC</td>
<td>UL</td>
<td>NC</td>
<td>UL</td>
<td></td>
</tr>
<tr>
<td>KK age (yrs)</td>
<td>11.9</td>
<td>12.9</td>
<td>13.1</td>
<td>14.4</td>
<td></td>
</tr>
<tr>
<td>creat (mg/dl)</td>
<td>0.7</td>
<td>0.76</td>
<td>0.75</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Uox (mmol/d)</td>
<td>n.d.</td>
<td>1.84</td>
<td>1.91</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Primary Hyperoxaluria Type II

Absence or decrease of Glyoxylate-Reductase

– Not liver specific

Less frequent (?) and with milder clinical course then type I

Elevated urinary excretion of oxalate (and L-glycercic acid)
Primary Hyperoxaluria Types 3 and possibly 4, 5, ...?

Typical clinical course and biochemical parameters

No enzyme defect in liver biopsy

No specific AGXT or GRHPR mutation

DHDPSL gene mutations in type III (Chr. 10)
Specific Diagnostics Evaluation

Repeated 24 h urine collections
Plasma oxalate determination
Mutation screening or
Liver biopsy
(prenatal diagnostic via linkage analysis)
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age</th>
<th>Ratio solute + creatinine</th>
<th>Urinary excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxalate</td>
<td></td>
<td>Mmol/mol/mg/g</td>
<td>&lt; 0.5 mmol/1.73m²/24 h</td>
</tr>
<tr>
<td></td>
<td>0- 6 months</td>
<td>&lt; 325-360/288-260</td>
<td>(&lt; 45 mg/1.73m²/24 h)</td>
</tr>
<tr>
<td></td>
<td>7- 24 months</td>
<td>&lt; 132-174/110-139</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2- 5 years</td>
<td>&lt; 98-101/80-95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5- 14 years</td>
<td>&lt; 70-82/60-65</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 16 years</td>
<td>&lt; 40/32</td>
<td></td>
</tr>
</tbody>
</table>
Specific Diagnostic Evaluation

Keep diagnosis in mind!

Diagnosis is often only made years after first symptom

> 30 % of patients are only diagnosed in end stage renal failure!
Median age at symptoms, diagnosis and follow-up per country
Outcome

<table>
<thead>
<tr>
<th></th>
<th>PH1</th>
<th>PH2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESRD at diagnosis</td>
<td>43%</td>
<td>0%</td>
</tr>
<tr>
<td>ESRD at follow-up</td>
<td>50.5%</td>
<td>4%</td>
</tr>
<tr>
<td>Died</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Missing data</td>
<td>69 of 501 (14%)</td>
<td>21 of 53 (40%)</td>
</tr>
</tbody>
</table>
Specific Treatment

Daily fluid intake > 3 Liter

– Via (naso)gastral tube in small infants and children

Pyridoxine in PH type I

Alkaline citrate or orthophosphate

Magnesium

Avoid diet with high oxalate content
AGXT Gene mutation:

28% Gly170Arg Phe152Ile

Favorable:
Pyridoxine declines oxalate excretion

Poor:

Prediction of outcome (kidney function)
## Survival of kidney function, for B6-responsive genotype

<table>
<thead>
<tr>
<th>Follow-up from birth (years)</th>
<th>Cumulative percentage preserved renal function</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>20</td>
<td>50%</td>
</tr>
<tr>
<td>40</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
</tr>
</tbody>
</table>

**Genotype**
- Gly170Arg or Phe152Ile
- Other genotype

**B6 mutations**
- Other mutation
- B6 mutation
- Other mutation-censored
- B6 mutation-censored
Specific Treatment

In renal failure early transplantation

No form of renal replacement therapy can remove sufficient amounts of oxalate

- Endogenous production 4-7 mmol/day
- RRT-elimination 6-10 mmol/week
Follow up of pre HD $P_{Ox}$ levels in PH I and non-PH patients
Transplantation

Only in pyridoxine sensitive patients

– Isolated kidney transplantation

Combined liver-kidney transplantation

- Sequential liver-kidney Tx

Pre-emptive liver transplantation
Problem: recurrence in the isolated kidney graft

- Mobilization of body oxalate stores (bone) with returning renal function after Tx
- Often mistaken for rejection
Awaiting further treatment options.....

Oxalobacter formigenes
- Currently phase III study

Small molecules (chaperones)
- Studies/Research ongoing

Hepatocyte transplantation
- Performed in other metabolic diseases

Gene therapy
Oxalobacter formigenes (Oxf): Oxalat degradierende Enzyme

Oxf metabolisiert Oxalat zu $\text{CO}_2 + \text{Formiat}$
Urinary oxalate excretion of 7 PH patients with normal renal function under Oxalobacter formigenes treatment

<table>
<thead>
<tr>
<th>Week</th>
<th>Urinary Oxalate (mmol/1.73 m²/24 h)</th>
<th>SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.50</td>
<td>± 0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Week-1</td>
<td>1.50</td>
<td>± 0.30</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Week-2</td>
<td>1.00</td>
<td>± 0.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Week-3</td>
<td>0.80</td>
<td>± 0.20</td>
<td></td>
</tr>
<tr>
<td>Week-4</td>
<td>0.80</td>
<td>± 0.20</td>
<td></td>
</tr>
</tbody>
</table>

* = p<0.01
** = p<0.001
The stone is not the disease itself, but only its leading symptom!
The primary hyperoxalurias are disastrous diseases!
Early diagnosis is therefore mandatory!