Diagnostic approach to hereditary renal hypouricemia

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Introduction – hypouricemia

- hereditary renal hypouricemia
  - hereditary xanthinuria

Characteristics of Czech patients

Problems of diagnosis

- incidence
  - dg. flow charts
Hypoexcretion of urate
4-component model of urate handling

glomerular filtration 100%
reabsorption 99%
post-secretory reabsorption 40%
urine excretion

secretion 50%
1%
51%
10%

Urate transporter
URAT 1- gene SLC22A12

• OMIM 607096, GeneID 116085
• 11q13, 2 transcript variants (3206 and 2940 bp)553 amino acids
• expressed in fetal and adult kidney
Hypouricemia < 119 µmol/l (2 mg/dL)

It is important to distinguish:

**Primary**
- Genetic defect - hereditary xanthinuria
- Transport defect - primary renal hypouricemia (RHUC1, RHUC2)

**Secondary**
- Increased renal secretion (Fanconi sy., Wilson’s disease)
- Medication (allopurinol, salicylates)
- Severe liver disease
- Thyrotoxicosis, diabetes mellitus, acute respiratory sy.
Hereditary xanthinuria

xanthine oxidoreductase (XO) deficiency  type I
XO def. + aldehyde oxidase deficiency  type II
molybdenum cofactor def.  ““ + sulfite oxidase def.

dg.markers: hypouricemia
high urinary concentration of xanthine

symptoms: cca 50% patients - hematuria, renal colic acute renal failure, crystalluria, urolithiasis

th: low purine diet, high fluid intake
(alkalization of urine is of no value)
Hereditary renal hypouricemia

- new transport defect of uric acid

- biochemical markers
  - hypouricemia ($S_{KM} < 120 \mu mol/l$)
  - increased excretion fraction of uric acid ($EF_{KM} > 10\%$)

- clinical features
  - urolithiasis
  - acute renal failure (exercise-induced)

RHUC 1 - URAT1 ($SLC22A12$ gene)
RHUC 2 - GLUT 9 ($SLC2A9$ gene)
Hereditary renal hypouricemia

mutation - gene SLC22A12
W258X- prevalent mutation

( patients with HPRT def., FJHN, APRT def, ASL def., ADA def.)

Are disorders with hypouricemia also in the Czech population?
Investigation of unexplained hypouricemia

exclusion of secondary causes of hypouricemia!

1. assessment of uric acid - serum, urine

2. urinary purine metabolites
   (+ allopurinol loading test)

3. molecular genetic analysis
   
   \textit{SLC22A12, SLC2A9}
   
   (in cooperation with Japan – \textit{SLC17A3, ABCC4, ABCG2})
Allopurinol loading test

patients with Xanthinuria type I - able

Xanthinuria type II - not able to metabolize allopurinol to oxipurinol

1. 300 mg of allopurinol (adults) …… after overnight fasting

2. Oxipurinol determined in plasma … after 1 hour

## Clinical and biochemical findings in patients with XDH deficiency

<table>
<thead>
<tr>
<th>case</th>
<th>age of dg. (years)</th>
<th>first sign</th>
<th>uric acid in serum (µmol/l)</th>
<th>Kaufman index (UA/Cr)</th>
<th>xanthine in urine (mmol/mol Cr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>3</td>
<td>hematuria</td>
<td>not detectable</td>
<td>0.002</td>
<td>598.0</td>
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<tr>
<td></td>
<td></td>
<td>renal stone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>8</td>
<td>hematuria</td>
<td>53.0</td>
<td>0.04</td>
<td>370.0</td>
</tr>
<tr>
<td>3.</td>
<td>9</td>
<td>none</td>
<td>16.0</td>
<td>0.08</td>
<td>327.0</td>
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<tr>
<td>4.</td>
<td>30</td>
<td>none</td>
<td>not detectable</td>
<td></td>
<td>180.0</td>
</tr>
<tr>
<td>controls</td>
<td></td>
<td></td>
<td>120-360</td>
<td>0.7</td>
<td>30.0</td>
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</tbody>
</table>
Clinical features and mutations (1-7th patients in SLC22A12 gene) and 8-9th patients in SLC2A9 gene

<table>
<thead>
<tr>
<th>case</th>
<th>sex</th>
<th>age yrs</th>
<th>UA µmol/l</th>
<th>FE$_{UA}$ (%)</th>
<th>ARF</th>
<th>urolithiasis</th>
<th>mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>f.</td>
<td>73</td>
<td>124</td>
<td>52.4</td>
<td>+</td>
<td>-</td>
<td>g. 8294-8302del</td>
</tr>
<tr>
<td>2.</td>
<td>f.</td>
<td>39</td>
<td>58</td>
<td>53.4</td>
<td>+</td>
<td>-</td>
<td>g. 82948302del/ g.9184C/T</td>
</tr>
<tr>
<td>3.</td>
<td>f.</td>
<td>53</td>
<td>78</td>
<td>60.3</td>
<td>-</td>
<td>-</td>
<td>g. 82948302del/ g.9184C/T</td>
</tr>
<tr>
<td>4.</td>
<td>m.</td>
<td>35</td>
<td>63</td>
<td>43.0</td>
<td>-</td>
<td>-</td>
<td>g. 8145G/C g.9214G/A</td>
</tr>
<tr>
<td>5.</td>
<td>f.</td>
<td>15</td>
<td>35</td>
<td>55.2</td>
<td>-</td>
<td>-</td>
<td>g. 8294-8302del g.9184C/T</td>
</tr>
<tr>
<td>6.</td>
<td>m.</td>
<td>5</td>
<td>95</td>
<td>52.6</td>
<td>-</td>
<td>+</td>
<td>1242-1250delGCTGGCAGGG</td>
</tr>
<tr>
<td>7.</td>
<td>m.</td>
<td>5</td>
<td>50</td>
<td>50.0</td>
<td>-</td>
<td>-</td>
<td>1245-1253delGGCAGGGCT</td>
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<tr>
<td>8.</td>
<td>f.</td>
<td>18</td>
<td>11</td>
<td>240.0</td>
<td>-</td>
<td>-</td>
<td>g. 43412_43413insC</td>
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<tr>
<td>9.</td>
<td>m.</td>
<td>23</td>
<td>10</td>
<td>220.0</td>
<td>-</td>
<td>-</td>
<td>g. 43412_43413insC</td>
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</tbody>
</table>
Clinical features (two UK patients with acute renal failure-ARF) and mutations in *SLC2A9* gene

<table>
<thead>
<tr>
<th>case</th>
<th>sex</th>
<th>age yrs</th>
<th>UA µmol/l</th>
<th>FE\textsubscript{UA} (%)</th>
<th>Cr µmol/l</th>
<th>ARF</th>
<th>mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>m</td>
<td>12</td>
<td>40</td>
<td>93.0</td>
<td>297</td>
<td>+</td>
<td>p.G216R; p.N333S</td>
</tr>
<tr>
<td>2.</td>
<td>m</td>
<td>14</td>
<td>58</td>
<td>53.4</td>
<td>202</td>
<td>+</td>
<td>p.G216R</td>
</tr>
</tbody>
</table>

- further evidence … ….. *SLC2A9* is a causative gene in RHUC2
- supports the prediction….both URAT1 and GLUT9 are essential for UA reabsorption

Renal hypouricemia - unrecognized disorder?

absence of $SLC22A12$ gene mutations in Greek Caucasian

Tzovaraz V. et.al. Scand J Clin lab Invest. 2007;67:589-95

5 patients (Macedonia), 2 (UK) – RHUC1 (URAT 1)

Tesic V. et.al. Plos One. 2011;6(12):e28641
EARLY DIAGNOSIS of INBORN ERRORS OF METABOLISM

1. available methods

2. proper indication

screening

newborn (PKU, hypothyreosis, etc.)

selective screening
- family history
- suspicious clinical signs

diagnostic guidelines
Dg. flow chart for unexplained hypouricemia
($S_{UA}: < 120 \, \mu\text{mol/l}$)

Evaluation of case history (urolithiasis, seizures, immunodeficiency)
Exclusion of secondary causes (drugs / allopurinol/, Fanconi sy. etc.)

1. Estimation of EXCRETION FRACTION OF UA

   if high $\rightarrow$ - mol.genet.analysis of URAT1, GLUT9

2. Urinary concentration of XANTHINE, S-SULFOCYSTEIN, THIOSULFATE

3. Urinary concentration of (DEOXY) GUANOSINE, (DEOXY) INOSINE

   if positive $\rightarrow$ - assay of purine nucleoside phosphorylase (PNP) in ery.
Dg.protocol allows to differentiate

a) XANTHINURIA (def.XO) (lithiasis, 50% of the patients are asymptomatic)

b) COMBINED DEFICIENCY OF XO/SULPHITE OXIDASE (seizures in newborns, evaluation od UA could be the first step to diagnosis)

c) PURINE NUCLEOSIDE PHOSPHORYLASE (defect of T-cell immunity)

c) HEREDITARY RENAL HYPOURICEMIA (lithiasis, high EF-UA)

d) Primary hypouricemia can be excluded ( ? new defect)
Diagnosis of hereditary renal hypouricemia

1. estimation of uric acid (UA) in serum
   - if less then 120 µmo/l

2. estimation of excretion fraction of UA
   - if high more than 10%

3. exclusion of other secondary causes of hyperuricosuric hypouricemia
   if excluded

4. molecular analysis of SLC22A and SLC2A9 genes
Conclusions

- hypouricemia → risk factor for kidney injury
  → indication for detailed purine metabolic investigation

- hypouricemia can be good diagnostic tool – enables to find asymptomatic patients

- available guidelines will help for early diagnosis of purine disorders with hypouricemia
Conclusions

- first patients with hereditary renal hypouricemia and xanthinuria were diagnosed in Czech population

- findings of a defect in the SLC2A9 gene provides further evidence that SLC2A9 is a causative gene in renal hypouricemia and support the prediction that normal function of both URAT1 and GLUT 9 are essential for normal uric reabsorption

- renal hypouricemia is still unrecognized disorder and probably not wide spread in Asia only