A Rare Cause of Renal Stone Formation in Two Siblings

Chris Stockdale

University Hospitals Bristol NHS Foundation Trust
Index case- patient A

- Born 2000
- Parents (first cousins) from Indian sub-continent
- Paternal Grandmother received dialysis for ESRF

- Possible UTI aged 18 months
  - Urea and electrolytes within reference ranges
  - Renal tract ultrasound showed right renal pelvis dilatation and echogenic debris in the right pelvis and bladder

- Followed up 1-2 yearly
  - Ultrasounds showed non-progressive pelvis dilatation
  - *E. coli* grown in several urine samples
February 2012

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>µmol/L</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>54</td>
<td>(39-60)</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>3.6</td>
<td>(2.5-6.5)</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>141</td>
<td>(133-146)</td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>104</td>
<td>(95-108)</td>
<td></td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>27</td>
<td>(22-29)</td>
<td></td>
</tr>
<tr>
<td><strong>Urate</strong></td>
<td>&lt; 20</td>
<td>(150-390)</td>
<td></td>
</tr>
</tbody>
</table>

August 2012

- Non obstructive 7 mm calculus at lower pole of right kidney detected by ultrasound scan
- Referral to Nephrology
January 13

• Low urate confirmed on repeat sample

• Investigations initiated for Xanthine Oxidase deficiency (Xanthinuria)
Purine metabolism

AMP → adenosine → inosine → hypoxanthine → xanthine → urate

IMP

Salvage Pathway

GMP → guanosine → guanine

Xanthine Oxidase

Xanthine Oxidase
Purine lab, St Thomas’

Urine

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Concentration (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urate</td>
<td>Not detected</td>
</tr>
<tr>
<td>Hypoxanthine</td>
<td>31</td>
</tr>
<tr>
<td>Xanthine</td>
<td>14</td>
</tr>
</tbody>
</table>

Normal metabolite ratio
90 urate : 5 hypoxanthine : 5 xanthine

Results consistent with Xanthine Oxidase deficiency
Stone formation in Xanthine Oxidase deficiency

AMP → adenosine → inosine → hypoxanthine → xanthine → urate

IMP → inosine

GMP → guanosine → guanine

Salvage Pathway

Xanthine Oxidase
Stone formation in Xanthine Oxidase deficiency

AMP
  ↓
adenosine

IMP
  ↓
inosine

hypoxanthine

GMP
  ↓
guanosine

guanine

xanthine

urate

STONES

Salvage Pathway

Xanthine Oxidase

Xanthine Oxidase
Xanthine oxidase

• Catalyses 2 oxidation reactions:
  – hypoxanthine to xanthine
  – xanthine to urate
  – coupled to the reduction of O₂ or NAD⁺

• The target of drugs to reduce hyperuricaemia (eg allopurinol)

• 1333 amino acid protein containing:
  – Molybdenum cofactor (sulphated)
  – Iron-sulphur centres
  – FAD cofactor
Metabolic causes of low urate, high xanthine

Xanthinuria type 1

Xanthinuria type 2

Molybdenum Cofactor deficiency
Metabolic causes of low urate, high xanthine

Xanthinuria type 1
• Mutations in Xanthine Oxidase gene
• Features may include renal colic, renal failure, haematuria, muscle pain
• May be asymptomatic

Xanthinuria type 2

Molybdenum Cofactor deficiency
Metabolic causes of low urate, high xanthine

Xanthinuria type 1
- Mutations in Xanthine Oxidase gene
- Features may include renal colic, renal failure, haematuria, muscle pain
- May be asymptomatic

Xanthinuria type 2
- Mutations in Molybdenum Cofactor sulphurase gene
- Xanthine Oxidase and Aldehyde Oxidase secondarily affected
- Clinically indistinguishable from type 1

Molybdenum Cofactor deficiency
Metabolic causes of low urate, high xanthine

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Molybdenum Cofactor deficiency
• Mutations in genes of Molybdenum Cofactor biosynthesis pathway
• Xanthine Oxidase, Aldehyde Oxidase and Sulphite Oxidase affected
• Severe neonatal presentation (microcephaly, psychomotor retardation)
Distinguishing Xanthinuria types 1 and 2

Type 1: Aldehyde Oxidase unaffected
Type 2: Aldehyde Oxidase activity reduced
Distinguishing Xanthinuria types 1 and 2

Type 1: Aldehyde Oxidase unaffected
Type 2: Aldehyde Oxidase activity reduced

1. Allopurinol loading test
   - Follow metabolism of allopurinol to oxopurinol by Aldehyde Oxidase
### Distinguishing Xanthinuria types 1 and 2

**Type 1: Aldehyde Oxidase unaffected**
**Type 2: Aldehyde Oxidase activity reduced**

1. **Allopurinol loading test**
   - Follow metabolism of allopurinol to oxopurinol by Aldehyde Oxidase

2. **Detection of endogenous products of Aldehyde Oxidase**

   ![Chemical Diagram](image)

   - N-methyl nicotinamide
   - N\textsuperscript{1}-methyl-2-pyridone-5-carboxamide
   - N\textsuperscript{1}-methyl-4-pyridone-5-carboxamide

   *Peretz et al* *Metabolomics* 8, 951-959 (2012)
Patient A

- Presence of nicotinamide metabolites in urine consistent with normal AO activity and therefore **Xanthinuria type 1**
• Homozygous for c.140dupG mutation in \( XO \) gene

• Results in a transcript encoding a 60 amino acid protein (wild type enzyme 1333 amino acids)

• Previously reported in an Afghan child with Biochemical results consistent with Xanthinuria type 1
Family studies

• One sibling with Biochemical results consistent with Xanthinuria type 1.
  – Homozygous for same mutation as index case

• Biochemistry of parents and other sibling not suggestive of Xanthinuria
  – all 3 are carriers of the mutation
Management

**Index case:**

Low purine diet and 3 L fluid intake per day

Surveillance by renal ultrasound

**Affected sibling:**

No evidence of renal stones on ultrasound

Optimise intake of clear fluid

Surveillance by renal ultrasound
A family with two cases of Xanthine Oxidase deficiency

Suggested by low urate in a patient with a renal calculus

Specialist Biochemistry and Genetic testing identified the cause as Xanthinuria type I

Family screening identified an affected sibling

Managed conservatively
## The major types of renal stone

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<thead>
<tr>
<th>Type</th>
</tr>
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<tbody>
<tr>
<td>Calcium oxalate</td>
</tr>
<tr>
<td>Calcium oxalate &amp; phosphate</td>
</tr>
<tr>
<td>Triple phosphate (magnesium, ammonium, calcium)</td>
</tr>
<tr>
<td>Uric acid</td>
</tr>
<tr>
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</tr>
<tr>
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# The major types of renal stone

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<tr>
<th>Stone Type</th>
<th>Associated Conditions</th>
</tr>
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<tbody>
<tr>
<td>Calcium oxalate</td>
<td>Hyperoxaluria, Hypercalciuria, Alkaline urine</td>
</tr>
<tr>
<td>Calcium oxalate &amp; phosphate</td>
<td></td>
</tr>
<tr>
<td>Triple phosphate (magnesium, ammonium, calcium)</td>
<td>Urea splitting bacteria</td>
</tr>
<tr>
<td>Uric acid</td>
<td>Diet, Increased cell turnover, Acidic urine</td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>Hypercalciuria, Alkaline urine</td>
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<td>Cystine</td>
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## The major types of renal stone

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<th>Type</th>
<th>Pre-disposing factors</th>
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Other pre-disposing factors: concentrated urine, low urine concentration of stone inhibitors (citrate, magnesium)
# Key investigations

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<th>Type</th>
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<tr>
<td>Serum/plasma</td>
<td>U &amp; E</td>
</tr>
<tr>
<td></td>
<td>Bicarbonate</td>
</tr>
<tr>
<td></td>
<td>Calcium (PTH)</td>
</tr>
<tr>
<td></td>
<td>Phosphate</td>
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<tr>
<td></td>
<td>Urate</td>
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<tr>
<td></td>
<td>Chloride</td>
</tr>
<tr>
<td></td>
<td>Magnesium</td>
</tr>
<tr>
<td>Spot urine</td>
<td>Microbiology</td>
</tr>
<tr>
<td></td>
<td>pH</td>
</tr>
<tr>
<td></td>
<td>Amino acids</td>
</tr>
<tr>
<td></td>
<td>Albumin</td>
</tr>
<tr>
<td>24 hour urine (acidified)</td>
<td>Calcium</td>
</tr>
<tr>
<td></td>
<td>Oxalate</td>
</tr>
<tr>
<td>24 hour urine (unacidified)</td>
<td>Urate</td>
</tr>
<tr>
<td>24 hour urine (acidified or unacidified)</td>
<td>Volume</td>
</tr>
<tr>
<td></td>
<td>Citrate</td>
</tr>
<tr>
<td></td>
<td>Sodium</td>
</tr>
<tr>
<td></td>
<td>Magnesium</td>
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Past essay questions

• Review the clinical biochemistry of renal stones.

• Outline the factors leading to the formation of renal stones. Discuss critically the techniques for the analysis of the content of renal stones.

• Give an account of the aetiology and pathogenesis of renal stones, and outline the investigations required in a patient presenting with renal stone disease.