A Rare Cause of Renal Stone Formation in Two Siblings

Chris Stockdale

University Hospitals Bristol NHS
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

Creatinine	54	µmol/L	(39-60)
Urea	3.6	mmol/L	(2.5-6.5)
Sodium	141	mmol/L	(133-146)
Chloride	104	mmol/L	(95-108)
Bicarbonate	27	mmol/L	(22-29)
Urate	< 20	µmol/L	(150-390)

August 2012

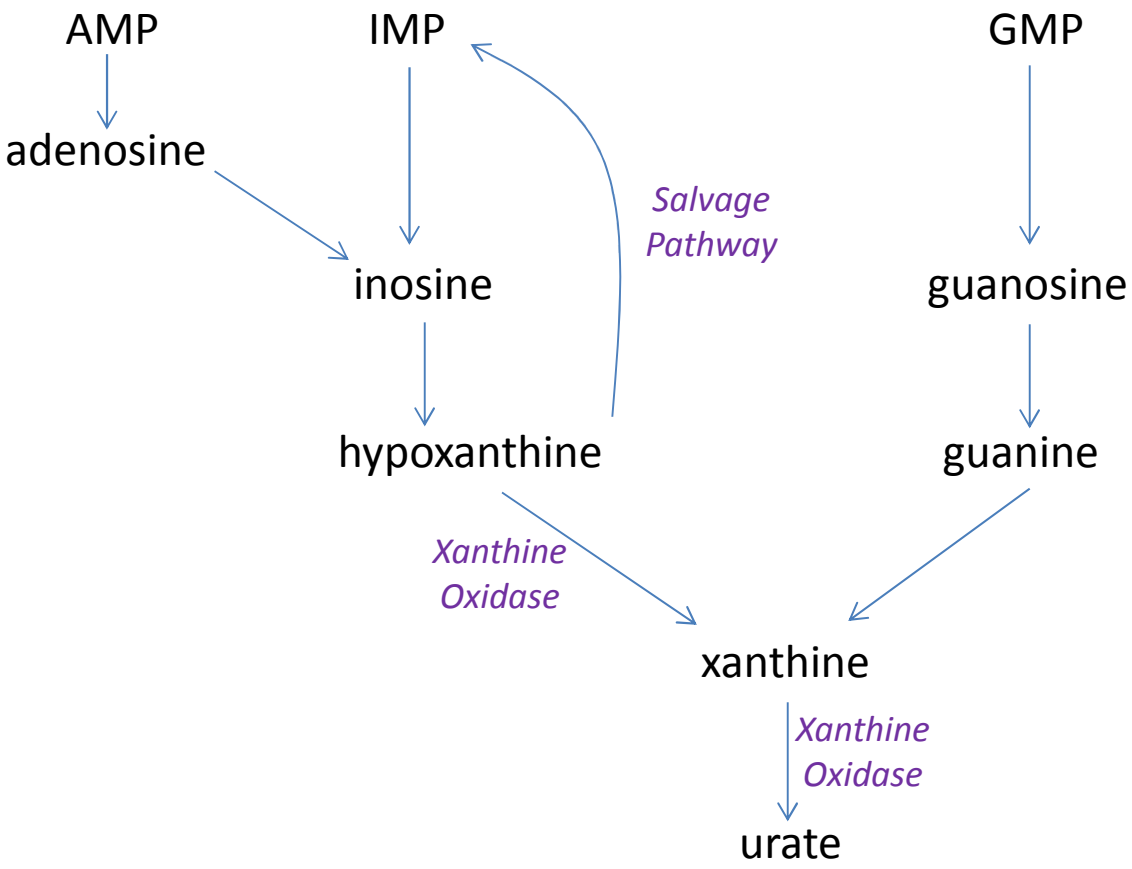
- Non obstructive 7 mm calculus at lower pole of right kidney detected by ultrasound scan
- Referral to Nephrology

January 13

- Low urate confirmed on repeat sample

- Investigations initiated for Xanthine Oxidase deficiency (Xanthinuria)

Purine metabolism



Purine lab, St Thomas'

Urine

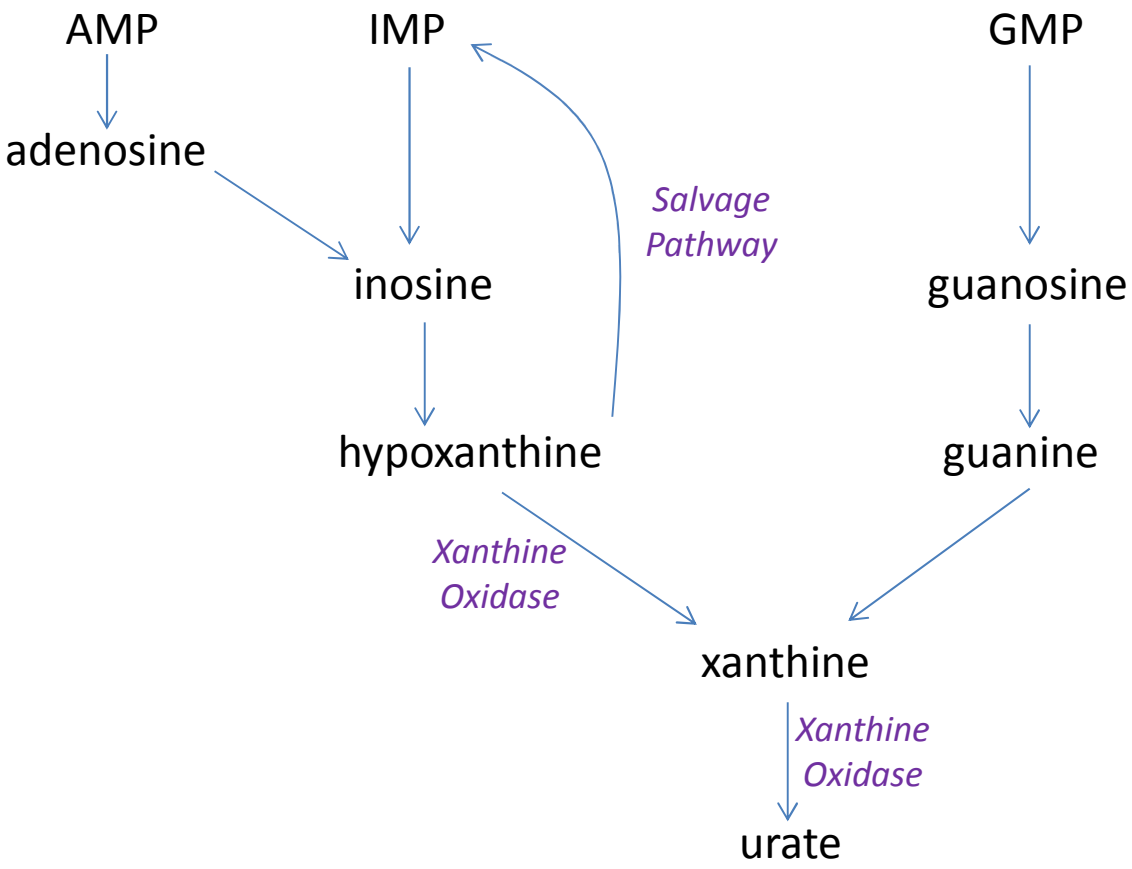
Metabolite	Concentration (mmol/L)
Urate	Not detected
Hypoxanthine	31
Xanthine	14

Normal metabolite ratio

90 urate : 5 hypoxanthine : 5 xanthine

Results consistent with Xanthine Oxidase deficiency

Stone formation in Xanthine Oxidase deficiency



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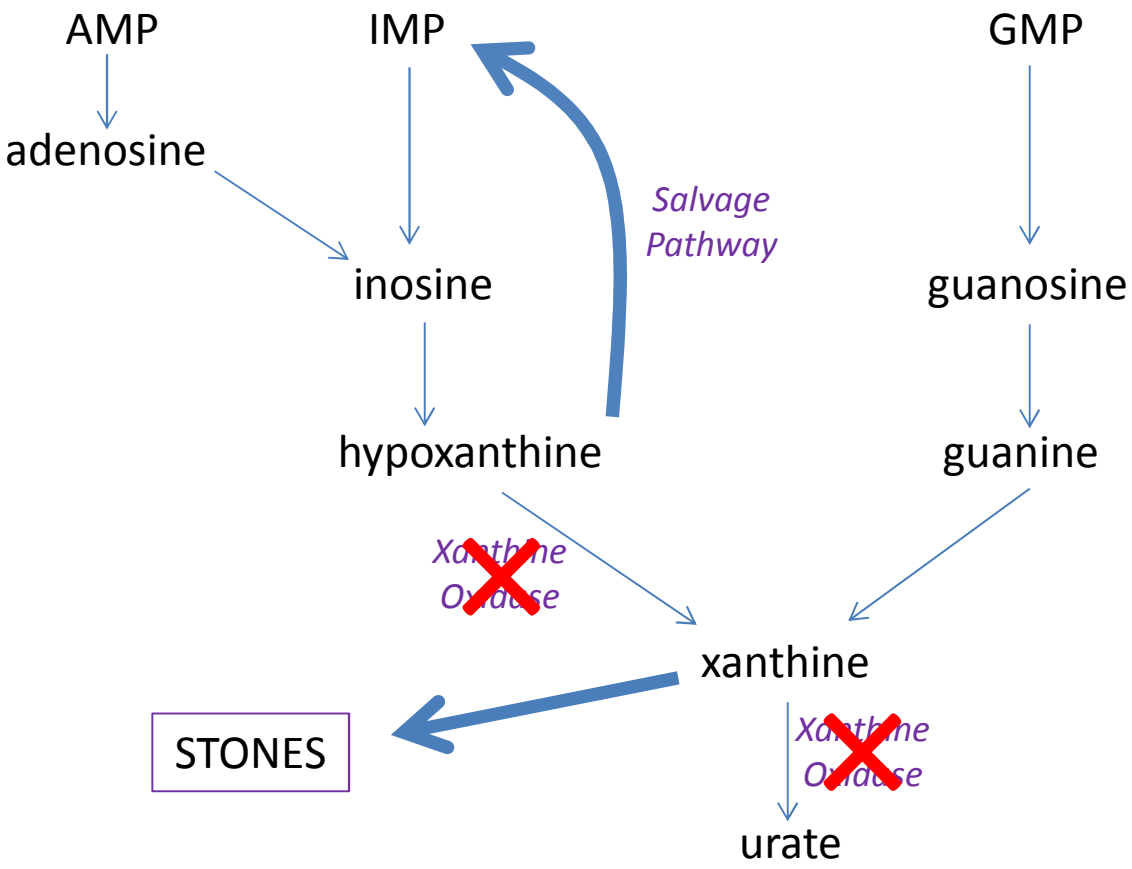
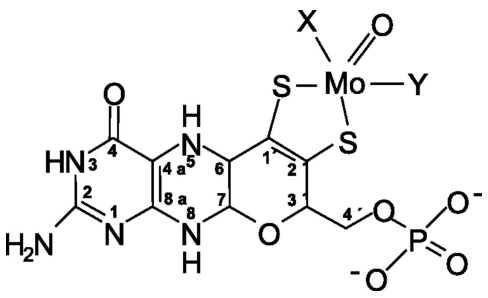


Xanthine oxidase

- Catalyses 2 oxidation reactions:
  - hypoxanthine to xanthine
  - xanthine to urate
  - coupled to the reduction of O_2 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

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- Mutations in Xanthine Oxidase gene
- Features may include renal colic, renal failure, haematuria, muscle pain
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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

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   - Follow metabolism of allopurinol to oxopurinol by Aldehyde Oxidase

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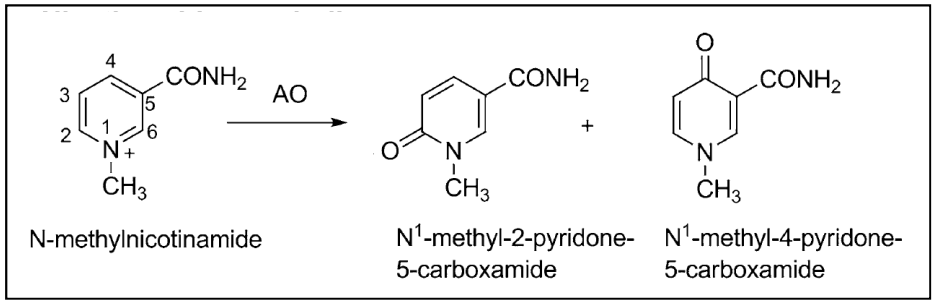
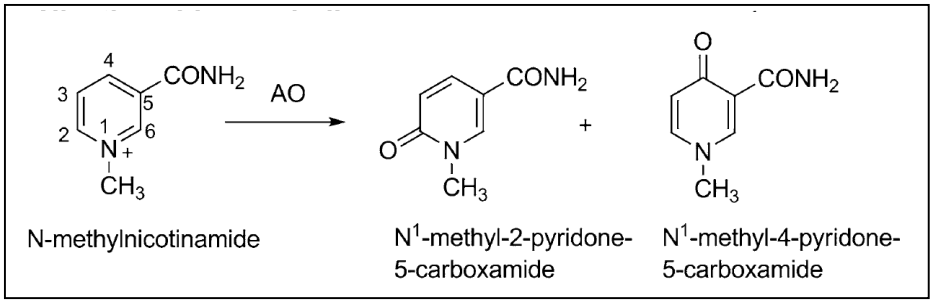
2. Detection of endogenous products of Aldehyde Oxidase



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**



Genetics (University of Prague)

- 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

Summary

- 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

Calcium oxalate Calcium oxalate & phosphate
Triple phosphate (magnesium, ammonium, calcium)
Uric acid
Calcium phosphate
Cystine

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Other pre-disposing factors: concentrated urine
low urine concentration of stone inhibitors (citrate, magnesium)

Key investigations

Serum/plasma	• U & E • Bicarbonate • Calcium (PTH) • Phosphate • Urate • Chloride • Magnesium
Spot urine	• Microbiology • pH • Amino acids • Albumin
24 hour urine (acidified)	• Calcium • Oxalate
24 hour urine (unacidified)	• Urate
24 hour urine (acidified or unacidified)	• Volume • Citrate • Sodium • Magnesium

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.