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Centre for Rare Diseases

Queen Elizabeth Hospital Birmingham NHS
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# APRT Deficiency – A Rare disease that should not be forgotten in renal failure of unknown cause

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## Overview

- An under recognized, autosomal recessive disorder of adenine metabolism that causes nephrolithiasis and kidney failure in a significant proportion of untreated patients.
- Patients lack the enzyme Adenine phosphoribosynltransferase, which causes the incomplete metabolism of adenine and this leads to an accumulation of 2,8 dihydroxadenine (2,8 DHA).
- Excretion via the kidneys leads to nephrolithiasis, crystalluria, and can cause crystalline nephropathy.

## Prevalence

- 0.5 to 1 per 100,000 in the Caucasian population,
- 0.25 to 0.5 per 100,000 in the Japanese population
- In Iceland, the estimated prevalence is 8.9 per 100,000
- Suggests there is a higher prevalence than is diagnosed
- Potential reasons for this:
- Lack of awareness of the disorder
- Inadequate evaluation of patients with kidney stones,
- Erroneous diagnosis of 2,8-dihydroxyadenine (2,8-DHA) stones as uric acid or xanthine stones, as all three of these types of stones are radiolucent

## Presentation

- Low GFR of unknown cause – can be AKI or progressive CKD
- History of stones
- Family history of kidney disease of unclear cause and/or stones
- Recurrent Renal Calculi (lucent)
- Progressive CKD (from crystalline nephropathy)
- ESRD of unknown cause
- Delayed Renal Allograft function

## Pathophysiology

- Recurrent urolithiasis is the most common feature – DNA crystals combine to form stones.
- Damage to kidney through tubular toxicity and precipitation of crystals within the tubules and interstitium – crystalline nephropathy (tubularinterstitial scarring).
- Deficiency of APRT enzyme is not corrected by transplantation - Recurrence of crystalline nephropathy in the graft causing loss of allograft function.

## Why is it under-recognised?

- Non specific presentation
- Sometimes presentation occurs with no stone history
- Stones are radiolucent so can be mistaken for uric acid stones
- Stone re-occurrence may not be properly investigated
- Biopsy can be unclear – crystals may not be interpreted correctly – erroneous diagnosis interstitial nephritis, or ATN
- Sometimes there are few crystals present so may be missed when biopsied
- No extra-renal symptoms occur in this disease

## Recognition and Diagnosis

- Full case history is vital – Past medical, social and family history
- Metabolic stone screening – useful to rule out stone forming disorders
- Stone analysis is important – requires infrared spectroscopy or x ray crystallography (standard biochemical processes fail to differentiate DHA from uric acid
- Definitive Diagnosis
- Diagnostic testing – red cell APRT assay sent to Purine lab
- Characterising crystals in urine (Crystalluria study) by light and polarising microscopy ** only in patients without severe kidney impairment
- Genetic analysis for APRT gene is possible but not easily available in UK

## Case 1

- 60 year old Asian male, referred for kidney transplant listing in 2010
- Background - chronic kidney disease, a history of kidney stones, treated with lithotripsy.
- The patient was transplanted in November 2015.
- Delayed allograft function.
- In total 4 biopsies (taken November to February); demonstrated progressive increase in calcium oxalate and crystals on biopsy.
- In March the patient was tested for APRT gene and found the patient to have Adenine phosphoribosyltransferase (APRT) deficiency.
- The patient was started on 100mg Allopurinol and increased to 200mg in May. The patient was unable to tolerate further dose increase and there appeared no improvement in renal function. Februxostat was added.

**May 2017**

- The patient is now 10 weeks off renal replacement therapy – e-GFR 14 ml/min

## Case 2

- 57 year old Caucasian female,
- Referred from GP, with AKI in May 2016.
- Recorded normal e-GFR of 63 ml/min/173^2, in February 2016.
- Presentation: mild symptoms of lethargy and nausea - e-GFR had deteriorated to 15ml/min/173^2.
- No recent history of ill health, no alcohol/ilicit drug use
- Biospy showed severe ATN and crystallisation.
- July – patient commenced on peritoneal dialysis and was being considered for transplantation.
- Urine oxalate tests returned back negative, so blood and urine sample sent to test for APRT deficiency.
- August 2016, a positive result for APRT deficiency was made.
- Patient was commenced on 150mg Allopurinol.
- Allopurinol was increased to 300mg once daily, and then to 400mg. Allopurinol was well tolerated
- September, renal function appeared to be improving, with pre dialysis creatinine of 230 mmol/l.
- In November, patient was trialled without renal replacement therapy.

**April 2017**

- Patient remains well, off any renal replacement therapy
- Latest e-GFR 19 creatinine, 227 mmol/l.

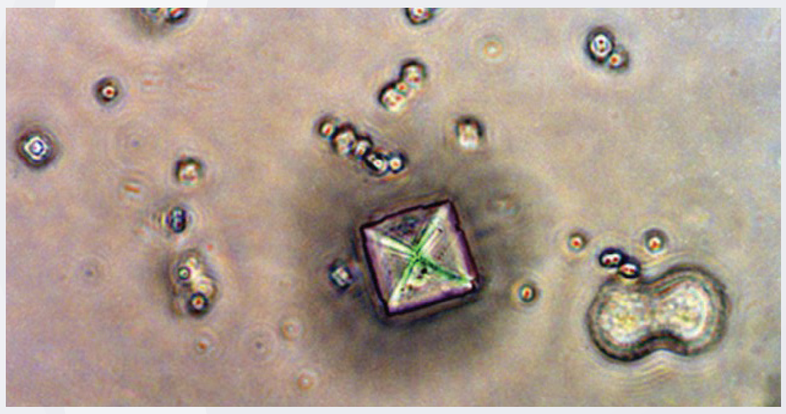


**Figure 1: Maltese cross pattern of DHA Crystals**

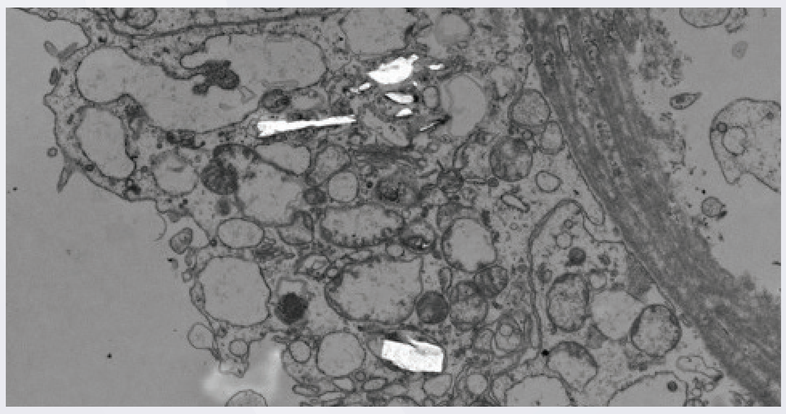
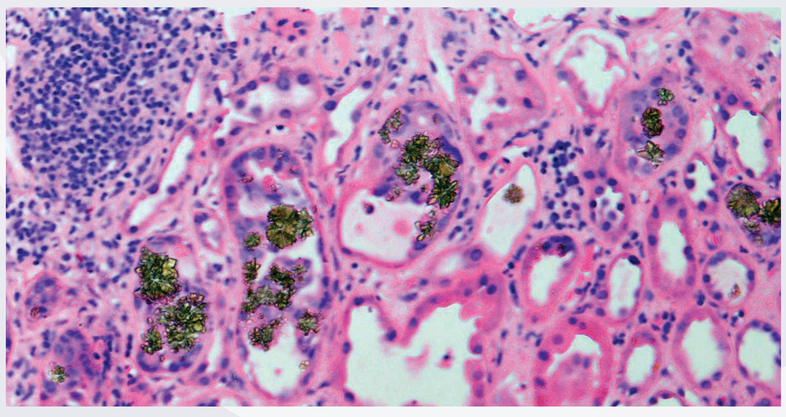
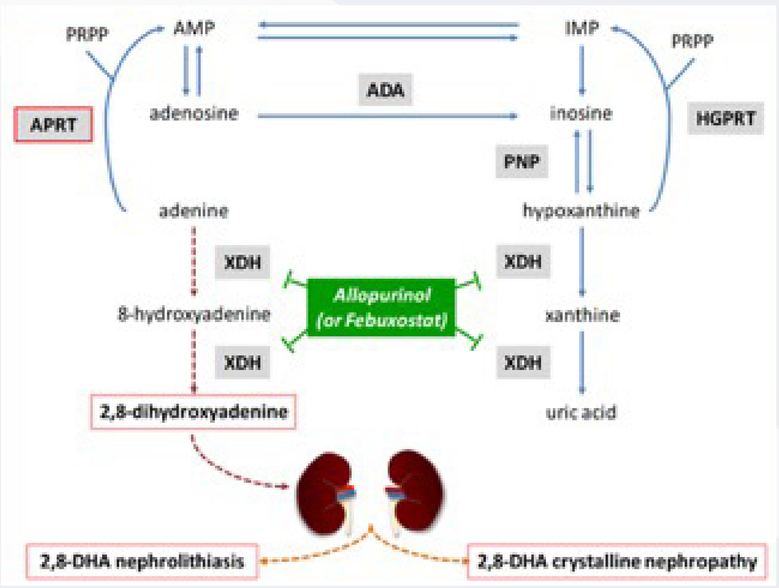


**Figure 2:**



**Case 1: Transplant biopsy slide**




**Metabolic flow diagram**

## Treatment

- Life long treatment with Allopurinol – purine analogue
- Inhibits activity of xanthine dehydrogenase, therefore blocking conversion of adenine into DHA.
  Dose – 200-600mg daily
  5-10mg/kg children
- Second line – februxostat (if allopurinol is not tolerated in sufficient doses)
- Fluid intake vital – 2.5 – 3 litres minimum (unless contra-indicated due to RRT)
- Urine alkalisation is not recommended as DHA crystals insoluble in high pH's
- Low purine diet – efficacy is questionable

## Surveillance

- Repeated quantitative anaysis of crystalluria is useful guide.
- Sustained fall in crystaluria is expected
- Dose of allopurinol can be titrated up if this is not obtained on initial dose.
- Monitoring of renal function and ongoing standard surveillance of patients with CKD is still key

## Disseminating and changing practice

- In Case Study 2 an awareness of APRT deficiency within the department and collaboration between departments increased the speed of diagnosis for this patient.
- Consider APRT in patients with progressive CKD and history of stones and/or family history of stones
- Consider consanguity and prevalence in those communities
- Education to nephrologists through conferences/education to increase awareness
- Education to transplant teams and clinicians involved in the work up of transplant patients, due to its reoccurrence in transplant grafts.

## Take home messages!

- Early identification and diagnosis appears key to the treatment and reversibility of renal dysfunction.
- Prompt initiation of treatment in case 2 lead to positive results and the patient is no longer dialysis dependant.
- Patients require higher doses of Allopurinol than usual accepted dose ranges in patients with compromised renal function.
- Transplant work up – caution in those with renal failure of unknown cause and stone history – consider screening for stone disease and APRT
- Progression of renal disease in APRT can be halted with prompt treatment of Allopurinol
- All is not lost! – transplant graft function may still be salvaged so it is imperative to take advice
- Good clinical and family history taking provides clues!!!

RareRenal
Information on rare kidney diseases

RaDaR

- **Renal Rare Disease Registry**
- **Encourage collaboration and provide research opportunities for the future**
- **Patient access to personal health information, test results**
- **Access to rare disease groups and information**

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