APRT Deficiency – A Rare disease that should not be forgotten in renal failure of unknown cause

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 phosphoribosyltransferase, which causes the incomplete metabolism of adenine and this leads to an accumulation of 2,8-dihydroxypurine (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.
- 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.
  - Ernennes diagnosis of 2,8-dihydroxypurine (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 stone passed.
- 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 allograft function.

Pathophysiology
- Recurrent uricosuria 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 (tubulointerstitial 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 crystalllography. 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.
- Febricourosis was added.

May 2017
- The patient is now 10 weeks off renal replacement therapy – eGFR 14 ml/min.

Case 2
- 57 year old Caucasian female.
- Refered from GP, with AKI in May 2016.
- Recorded normal e-GFR of 65 ml/min/1.732 in February 2016.
- Presentation: mild symptoms of lethargy and nausea - eGFR had deteriorated to 15ml/min/1.732.
- No recent history of ill health, no alcohol/illicit drug use.
- Biopsy 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.
- Patient was well tolerated.
- September, renal function appeared to be improving, with pre dialysis creatinine of 235 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.

Treatment
- Life long treatment with Allopurinol – purine analogue.
- Inhibits activity of xantathine 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).
- Urate alkalinisation is not recommended as DHA crystals insoluble in high pH.
- Low purine diet – efficacy is questionable.

Surveillance
- Repeated quantitative analysis of crystalluria is useful guide.
- Sustained fall in crystalluria 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 doses 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!!!

Case 1: Transplant biopsy slide

Figure 1: Maltese cross pattern of DHA Crystals

Figure 2: