Adenine phosphoribosyltransferase deficiency in the United Kingdom: two novel mutations and a cross-sectional survey

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Abstract

Background: Adenine phosphoribosyltransferase deficiency is an inborn error of metabolism that can cause kidney disease from crystalline nephropathy or kidney stones.

Methods: We present three cases from a single centre with varied presentations to illustrate how increasing awareness led to better patient identification. We then undertook a cross-sectional survey of all the patients identified from the Purine Research Laboratory in the UK since 1974.

Results: Our index case presented with recurrent nephrolithiasis and was diagnosed on stone analysis, the second case presented with acute kidney injury and the third case was identified from a biopsy undertaken for acute on chronic kidney injury. Genetic studies identified two novel mutations. Twenty patients were retrospectively identified. The mean age at diagnosis was 25 years (range 2–70); eight were <20 years, seven were 20–40 years and five were >40 years. Five of the 20 patients were deceased, 3 after end-stage renal disease (ESRD). Twelve have normal renal function, one had CKD stage 3, one had severe kidney disease and one was on dialysis.

Conclusions: Adenine phosphoribosyltransferase deficiency presents in a wide spectrum in all age groups. Patients can be completely asymptomatic and kidney disease may be incorrectly attributed to other conditions. Outcome is poor in late diagnosis and there is a high prevalence of ESRD. Patients with unexplained renal stone disease or deterioration in kidney function should be considered for screening. Identification and surveillance of patients in the UK can improve. There is now a rare disease registry with meetings organized that include patients, families and health care providers to improve awareness.

Key words: adenine phosphoribosyltransferase deficiency, chronic kidney disease, kidney stones, outcomes
Introduction

Adenine phosphoribosyltransferase (APRT) is a purine salvage enzyme that catalyzes the formation of 5'-adenosine monophosphate and pyrophosphate from adenine and 5'-phosphoribosyl-1-pyrophosphate. A partial deficiency of the enzyme was first reported in 1968 in a family where the index case was identified as part of a control series from 150 patients [1]. The first patient with complete deficiency was reported in 1974 [2]. Subsequent case reports and a report of a family with complete APRT deficiency [3–5] helped characterize this disorder by the presence of excessive urinary amounts adenine, 8-hydroxyadenine and 2,8-dihydroxyadenine (2,8-DHA). 2,8-DHA is formed by the action of xanthine dehydrogenase on adenine, and nephropathy occurs due to its excretion and crystallization due to its low insolubility in urine [5, 6] (Figure 1). Treatment is with a xanthine dehydrogenase inhibitor such as allopurinol [5]; hydration and dietary purine restriction may also add some benefit. A second form of APRT deficiency has been described in the Japanese population [7, 8] where some APRT enzyme activity (10–25%) is detectable on red cell lysate studies.

The APRT gene is located on chromosome 16q24 and the condition is inherited in an autosomal recessive manner. The mutation rate of APRT in Caucasians is estimated to be 0.4–1.2% and the homozygous rate is 1 in 50 000 to 1 in 100 000 [9, 10]. It is well reported in the paediatric literature [11], but there is increasing knowledge that many patients present to adult services. The disease has been well characterized in the Japanese and Icelandic populations [7, 12]. Heterogeneous cohorts from France and the APRT Deficiency Registry of the Rare Kidney Stone Consortium have shown poor outcomes with a delayed diagnosis [13, 14]. Delays in diagnosis can occur because patients may be asymptomatic, especially at a younger age, or because appropriate investigation of recurrent urolithiasis has not been undertaken. The overall UK experience is poorly reported and is similar to the experience reported from the USA, where only a handful of cases have been described in the literature [15–17].

Patients can present with urolithiasis or crystalline nephropathy, which can present with acute kidney injury (AKI) or chronic kidney disease (CKD). In this report, we describe three cases identified from a single centre in the UK with a full spectrum of

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**Figure 1.** Diagram showing the adenine salvage pathway. Lack of salvage by APRT causes accumulation of adenine and production of 2,8-dihydroxyadenine by the action of xanthine dehydrogenase. PRPP, phosphoribosyl pyrophosphate; APRT, adenine phosphoribosyltransferase.

**Table 1.** Details of follow-up survey from patients diagnosed at the Purine Research Laboratory, St Thomas’ Hospital

| No. | Age at diag./sex | Ethnicity | Diag. year | Reason for testing | Urological procedure | Renal outcome (eGFR using CKD-EPI for adults) and last follow-up where stated |
|-----|------------------|-----------|------------|-------------------|---------------------|--------------------------------------------------------------------------------|
| 1   | 4/F              | Caucasian | 1979       | UTIs and renal stone | Unknown             | Txp – HD – deceased                                                                   |
| 2   | 24/M             | South Asian | 2003      | Transplant biopsy  | Unknown             | Unknown – HD – deceased                                                                |
| 3   | 28/F             | South Asian | 2003      | FH (sister of pat.2) | Unknown             | CKD stage 3 (Cr 112, eGFR 58, 2009)                                                   |
| 4   | 2/M              | Caucasian  | 2004       | UTIs and renal stone | Ureretic stenting  | Normal (2014)                                                                         |
| 5   | 14/M             | South Asian | 2006      | Renal stones       | Unknown             | Normal                                                                              |
| 6   | 42/M             | Caucasian  | 1998       | Renal stones       | Unknown             | Normal (Cr 98, eGFR 82, 2012)                                                         |
| 7   | 45/M             | Caucasian  | 1997       | Renal stones       | Unknown             | Deceased                                                                            |
| 8   | 43/F             | Caucasian  | 1997       | Renal stones and FH (sister to 7) | Unknown             | PD – HD – Deceased                                                                   |
| 9   | 3/F              | Caucasian  | 2002       | UTIs and renal stone | Ureretic stenting  | Normal (Cr 45, 2012)                                                                  |
| 10  | 3/M              | South Asian | 1987      | Renal stones       | Unknown             | Normal (Cr 67, 2004)                                                                  |
| 11  | 31/M             | Portuguese | 2011       | Renal stones       | Ureretic stenting  | Normal                                                                              |
| 12  | 70/M             | South Asian | 2013      | Renal stones       | Ureteroscopy and stone removal           | CKD stage 4 (Cr 283, eGFR 19, 2005)                                                     |
| 13  | 39/M             | Caucasian  | 2010       | Renal stones       | Ureteroscopy and stone removal           | Normal (Cr 107, eGFR 75, 2011)                                                        |
| 14  | 40/M             | Caucasian  | 2013       | Native biopsy      | None                 | Deceased (Last Cr 262, eGFR 23, 2016)                                                 |
| 15  | 31/M             | South Asian | 2004      | Renal stones       | Ureteroscopy and stone removal           | PD – HD                                                                              |
| 16  | 4/F              | South Asian | 2011      | Renal stones and FH | None                 | Normal (Cr 38, 2013)                                                                  |
| 17  | 6/F              | South Asian | 2011      | Renal stones and FH | None                 | Normal (Cr 40, 2014)                                                                  |
| 18  | 30/M             | South Asian | 2012      | AKI and FH         | None                 | Normal (Cr 103, eGFR 84, 2013)                                                        |
| 19  | 27/M             | South Asian | 2012      | FH                 | None                 | Normal (Cr 102, eGFR 86, 2008)                                                        |
| 20  | 3/M              | South Asian | 2014      | Renal stones and FH | Open removal of stone                  | Normal (Cr 24, 2014)                                                                  |

Individuals in shaded rows are patients diagnosed recently at our centre. Diag., diagnosis; UTI, urinary tract infection; FH, ; Txp, ; HD, haemodialysis; Cr, creatinine; PD, peritoneal dialysis.
presentations. We then conducted an outcome survey of all cases identified by the Purine Research Laboratory at St Thomas’ Hospital, UK (Table 1).

Materials and methods

Case histories

Case 1 (index case): Chronic kidney disease with recurrent stone disease. An 18-year-old man of Pakistani origin presented with left renal colic and a serum creatinine of 216 µmol/L (reference range 60–110). He had psoriasis and smoked 10 cigarettes a day but was otherwise generally fit and well. Intravenous urography demonstrated a delayed left nephrogram with a partial obstruction. He underwent extracorporeal shock wave lithotripsy (ESWL) but no stone fragments were sent for analysis and no urine studies for crystals were done. He was lost to routine follow-up but re-presented 4 years later; stone analysis following ESWL on that occasion showed a crystalline 12 mg stone consisting of 2,8-DHA crystals. APRT activity was not detected in red cell lysates. He returned to Pakistan and took herbal medication for intermittent renal colic. He then re-presented after 10 years with loin pain and computed tomography (CT) of the kidneys, ureters and bladder (KUB) showed a persistent stone and atrophic kidney on the left side (Figure 2). He failed to attend follow-up and only presented to clinic when a blood test by his general practitioner showed a serum creatinine of 392 µmol/L. He was started on allopurinol, but was poorly adherent to treatment; the dose was titrated up to 300 mg once a day with undetectable urine 2,8-DHA on repeat testing. He developed end-stage renal disease (ESRD) and was on peritoneal dialysis for 2 years before switching to haemodialysis for recurrent peritonitis, and continues to take allopurinol. He had a strong family history of stone formers; two of his three children were affected by recurrent stone formation. APRT deficiency was confirmed using red cell enzyme studies. DNA analysis revealed a homozygous novel mutation in the APRT gene, c.543A>T, p.181X>C.

Case 2: Recurrent AKI and urolithiasis. A 22-year-old patient of Pakistani origin presented with back pain and AKI with a serum creatinine of 312 µmol/L. He was on a course of a non-steroidal anti-inflammatory drug (NSAID) following a recent knee arthroscopy. A diagnosis of NSAID nephropathy was presumptively made on the finding of microscopic haematuria and prompt resolution of AKI with intravenous fluids. He failed to attend follow-up but had another presentation 2 years later with back pain and microscopic haematuria; intravenous urogram was normal and serum creatinine was 114 µmol/L. He then presented 8 years after his initial presentation with back pain and a serum creatinine of 418 µmol/L. He had mild urine abnormalities [urine microscopy red blood cell (RBC) count 8 × 10^6/L and urine protein:creatinine ratio 55.1 mg/mmol], no formal urine microscopy for crystals was undertaken at any stage and CT KUB was unremarkable. The renal team was aware that he was the brother of the index case. A renal biopsy showed a crystal nephropathy with interstitial nephritis and tubular deposition of crystals (Figure 3). APRT deficiency was confirmed on red cell enzyme studies and allopurinol was started. The family tree of Cases 1 and 2 are shown in Figure 4. The patient does not attend clinic regularly but appears adherent with treatment. His son also had a history of renal stones in infancy with APRT deficiency confirmed on red cell studies. The remainder of the family were offered genetic screening but have declined testing. A third brother already had complaints of renal colic but has not sought treatment. Although a formal diagnosis of APRT deficiency has not been confirmed, we encouraged the use of allopurinol 100 mg once a day, as this diagnosis was most likely.

Case 3: Acute on chronic kidney injury in a diabetic patient. A 48-year-old man with hypertension, pernicious anaemia and a 7-year history of type 2 diabetes was referred to the renal services with an acute decline in renal function (serum creatinine of 131–348 µmol/L). He was on insulin, metformin, simvastatin, perindopril and vitamin B12 injections. His perindopril and metformin were stopped. He did not have a history of kidney stones and was otherwise well. His urine protein:creatinine ratio was 18 mg/mmol (albumin:creatinine ratio 3.27 mg/mmol) and microscopy showed an RBC count of 5 × 10^6/L; no crystalluria was noted. A renal biopsy showed minimal diabetic features but marked tubulointerstitial nephritis with crystal deposition, suggesting a crystalline nephropathy (Figure 3). APRT activity was not detected in red cell lysates and treatment with allopurinol 100 mg once a day was started. Genetic studies revealed a novel homozygous APRT mutation, c.380A>G, p.I127D>C. There was no history of renal stone disease in the family; his sister was heterozygous for the mutation. He died 3 years after presentation due to complications related to a brainstem tumour; his creatinine was 262 µmol/L at the time.

Retrospective survey

We identified all the patients who were diagnosed with APRT deficiency at the Purine Research Laboratory at Guys and St Thomas’ Hospital (London, UK), a national referral centre for disorders of purine metabolism. Patients from 1974 onward were identified using computerized and paper records. Patients were diagnosed using urine samples and whole blood ethylenediaminetetraacetic acid samples. Genetic studies were done on the more recent patients diagnosed from our centre. Patients are not followed up by the Purine Research Laboratory and we therefore sought up-to-date information on patients by contacting the initial referring centre. Due to the historical nature of the information, we only sought basic outcome data obtainable from electronic records. Most centres did not have access to notes, as they had been destroyed or were not easily accessible.

Biochemical and genetic analysis

The estimated glomerular filtration rate (eGFR) was calculated using Chronic Kidney Disease Epidemiology Collaboration...
Urinalyses for crystalluria were not undertaken in any of the cases. Ultrapure liquid chromatography was used to detect the presence of 2,8-DHA in the urine. APRT activity was measured in red blood cell lysates. DNA was extracted from blood to detect mutations on the APRT gene. DNA studies were extended to other family members.

Fig. 3. Native kidney biopsies. (A) Native renal biopsy from case 2 showing tubular crystalline deposits of 2,8-dihydroxyadenine with inflammatory changes suggestive of tubular interstitial nephritis (×400 magnification). (B) Biopsy shown under polarizing light demonstrating birefringence (×400 magnification). (C) Native kidney biopsy from case 3 showing marked scarring with mild diabetic changes (×100 magnification). (D) Chronic inflammatory changes around crystalline deposits are also present (×250 magnification).

Fig. 4. Family tree of case 1 (index case arrowed) and case 2. A third brother was diagnosed in the community. The three known affected siblings did not attend regular outpatient appointments; our index case became more adherent when he was symptomatic with renal failure and was approaching dialysis. The remaining two siblings have not come forward for screening with urine testing. Consanguinity is shown and awareness of the carrier status of offspring and the wider family will allow early treatment for future generations.
Stone analysis
Stone analysis consisted of morphologic examination by stereo-microscope and infrared spectroscopy.

Pathological analysis
Standard processing of native kidney biopsies includes light microscopy, immunohistochemistry and electron microscopy. Stains for light microscopy included haematoxylin and eosin, periodic acid-Schiff and Congo red. Stains for immunohistochemistry consisted of IgG, IgM, IgA, C3c, C1q, C9 and fibrinogen. Crystals in the biopsy were examined under polarizing microscopy.

Results
Renal biopsy findings
A native kidney biopsy in the second case had two cores sampling 43 glomeruli. Eight were obsolete; there was patchy tubulitis and mild tubular atrophy with polarizable crystalline material seen in and around the tubules. There was also mild interstitial scarring and a chronic inflammatory cell infiltrate with occasional eosinophils. Features were of a crystal nephropathy with superadded acute interstitial nephritis (Figure 3).

Native kidney biopsy from the third case with a history of diabetes showed only four glomeruli. None were obsolete and they showed mild diabetic changes of mesangial expansion and capillary loop thickening. There was marked tubular atrophy with advanced interstitial scarring and areas of chronic and acute inflammation consisting of discrete granulomata with multinucleate giant cells centred on foreign body crystalline deposits and occasional eosinophils (Figure 3). The decision to screen for APRT was based on the findings of crystals, something that we would not have undertaken if we had not seen the second case.

Serum creatinine trends
The graph from our index case shows progression of CKD with episodes of recurrent nephrolithiasis (Figure 5a). His first presentation was at the age of 18 years, but there was a significant delay to diagnosis. Treatment with allopurinol may have delayed his progression to ESRD.

The renal function in our second case resolved back to baseline (Figure 5b). Although he does not engage with the renal services, we are informed via his older brother that he is adherent with his allopurinol treatment.

The third case was biopsied for an acute on chronic decline in renal function and testing from APRT deficiency was undertaken in view of histology. Once treatment was initiated his renal function improved significantly (Figure 5c).

Retrospective survey results
Most of the clinicians who initially cared for the historically diagnosed patients are no longer at the referring department. Many patients are not under regular follow-up, but most had some tests of renal function available. Paediatric patients had good follow-up by the paediatric services but there were some patients who had made the transition into adult services and were lost to follow-up.

Fig. 5. Trends in serum creatinine. (A) Graph showing the trend in creatinine from our index case with some stabilization of kidney function after initiating allopurinol (arrowed) before eventually reaching ESRD. (B) Graph showing resolution of AKI in case 2 from both presentations treated with intravenous fluids. (C) Graph showing the trend in serum creatinine in case 3 with improvement of renal function following initiation of allopurinol (arrow).
There were 20 cases in total from 13 families. Six of the 20 patients were our local recently diagnosed cohort, otherwise there were few new cases diagnosed, with 13 patients diagnosed over 34 years. The most common reason for testing was nephrolithiasis (15/20); there were two cases diagnosed due to siblings with the condition and two patients had findings on biopsy (one transplant) that led to testing. Fourteen of the 20 were male and the mean age at diagnosis was 25 years (range 2–70). Seven patients had known urological intervention; urological history was difficult to ascertain on the remaining patients due to the difficulties mentioned above. There are a disproportionately high number of South Asian patients in our cohort; two of these families had a known history of consanguinity.

Five patients are deceased; three were known to have ESRD, one had CKD stage 4 and it is unclear if the remaining deceased patient had CKD. Of the 15 surviving patients, 1 was on dialysis, 1 had severe kidney disease and 1 had CKD stage 3. The median creatinine at the last follow-up in patients (where available) was 91 µmol/L (range 24–282). Patients diagnosed as adults had worse outcomes, with 4 of 12 patients deceased, 2 of these after onset of ESRD.

Discussion

APRT deficiency is a rare disease characterized by excessive urinary excretion of 2,8-DHA leading to stone formation and nephropathy, either from an obstructive nephropathy or a crystalline nephritis. The crystalline nephritis in APRT nephropathy can be acute or chronic and the more specific term ‘DHA nephropathy’ has been suggested. We report on three cases that illustrate the spectrum on presentation, with two biopsies showing findings of acute and chronic inflammatory changes. Our retrospective analysis shows that nephrolithiasis was the most common reason for testing and that diagnosis later in life was associated with worse outcome. We identified two novel mutations that abolished APRT activity.

Most cohort data for this condition come from Japan, Iceland and France [7, 12–14]. The evidence suggests that most patients are not detected sufficiently early, if at all, to institute effective treatment and prevent renal injury. There are significant delays in diagnosis from the first presentation and some patients can be asymptomatic.

We report three cases from a medium-size centre in the UK that illustrate some important points and difficulties in managing these patients. There was a delay in diagnosis in our first case, as stone analysis was not undertaken. Patient follow-up and treatment adherence was poor, a pattern reported by clinicians in our survey among young patients who feel very well in-between episodes of urolithiasis. Our first patient had severe kidney disease by the time he eventually presented to the renal service. Treatment and ensuring adherence may have helped preserve residual kidney function while on dialysis. He was on allopurinol 300 mg/day with undetectable 2,8-DHA, but higher doses in the range of 300–800 mg/day with a gradual titration up may have helped preserve and improve kidney function further [12].

Our second case had two presentations to the medical services before the diagnosis was made. He was eventually investigated by the renal team, as he was the brother of our index case, highlighting the importance of screening siblings and awareness of family members about the potential diagnosis. Our third case was an incidental finding; although he had a history of diabetes, a biopsy was undertaken since there was no clear clinical explanation for the acute decline. There have been reports of asymptomatic patients in a recent cohort [14] who have developed kidney disease, and our biopsy findings suggest a chronic crystalline nephropathy with minimal urine abnormalities. A recent series of diabetics with kidney biopsies showed that >36% had non-diabetic kidney disease and 27% had diabetic disease along with other pathology [18]. It is unclear in this study if this led to any changes in treatment, but our patient benefited from making this diagnosis based on the biopsy finding of crystals. This case illustrates the importance of using polarized light when analysing crystals in biopsies of patients with CKD.

The diagnosis of APRT deficiency is rare but our study shows it is almost certainly being under-diagnosed. This is in keeping with previously published data. Diagnosis is late in the majority of patients and this appears to be associated with adverse outcomes. Most testing is undertaken ad hoc, thus the experience of the treatment centre will play a role in patient identification. It is unclear how many of our cohort of patients had stone analysis that may have prompted testing. Stone testing in the UK is not robust and it is unclear if all centres use a full infrared spectroscopic analysis to differentiate between uric acid and 2,8-DHA stones. Our experience is that the care of recurrent stone formers in the UK is disjointed and many patients do not have appropriate metabolic assessments to reduce the likelihood of future stone formation. 2,8-DHA excretion in the urine was the most useful screening and diagnostic test undertaken by the Purine Research Laboratory.

Our cohort consists of a large number of South Asian patients and this ethnic group was disproportionately represented compared to the overall UK population. This may suggest that this ethnic group has a predisposition to a higher frequency of mutation, but it may be due to increased rates of consanguinity [19]; two families in our cohort had known consanguinity. Our study is also in line with previous studies suggesting that late diagnosis is associated with worse outcome, reinforcing the findings from the French experience [13] and recent data from the APRT Deficiency Registry of the Rare Kidney Stone Consortium [14], but our patient numbers are small.

The majority of patients presented to adult services, thus adult nephrologists should be vigilant for this diagnosis. Diagnostic algorithms when stone analysis is not available suggest using crystalluria to screen potential patients with an unknown cause of CKD, acute on chronic kidney disease, acute allograft dysfunction or a history of stone formation [20, 21]. Crystalluria was not done in our cases and today’s laboratory urinary studies are automated and formal microscopy is operator dependant, with poor experience in small to medium centres. Furthermore, crystals should be examined by Fourier transform infrared microscopy. The cost of screening patients who may present without renal stones should be evaluated in a cost–benefit study, as the number of patients eligible for screening may be very large. We would suggest screening patients with recurrent loin pain. Clinicians should also be aware that an alternative clinical diagnosis may have been incorrectly attributed as the cause of AKI or CKD.

The other key method of diagnosis is testing siblings of patients and, if there is a history of consanguinity, other members of the family. Many patients in our cohort were lost to follow-up from the initial referral centre for different reasons, but follow-up is important for counselling of siblings and other family members that may be heterozygous for mutations. Any family member that develops kidney disease or symptoms suggestive of nephrolithiasis should be offered testing to prevent unnecessary morbidity and mortality. Adult nephrology services should be aware that patients with a positive siblings (or a family history
if consanguinity is suspected) of recurrent kidney stones can present with CKD or AKI. Nephrologists should also be aware that concurrent pathology may occur in both AKI and CKD (Table 2).

APRT deficiency is one of the few stone-forming conditions where the pathological process has been elucidated and specific treatment greatly improves outcome. Treatment is cheap and will reduce the morbidity and mortality associated with recurrent stone formation and CKD. We have described three cases that illustrate the spectrum of renal presentations of APRT deficiency and where increasing experience led to more cases being diagnosed. Our retrospective analysis of cases in the UK showed a high prevalence of ESRD and poor outcome with late diagnosis. Every effort must be made to find such cases, as it is an easily treatable disease associated with significant morbidity and mortality. Adult nephrologists should be aware of the diagnosis, as most patients present late. Better strategies have to be in place to find patients, including diligent stone and urine analysis in recurrent stone formers, screening siblings and informing family members of known patients and using polarized light for crystal analysis in biopsy studies, even if another pathology is present. Detecting asymptomatic patients may be difficult and there may be a case for screening patients with kidney disease and no or low-grade proteinuria, but there has to be a cost–benefit assessment before this can be formally recommended.

Acknowledgements
We thank Dr G. Rumsby, Consultant Biochemist, University College Hospital; Dr S. Roe and Dr C. Byrne, Consultant Nephrologists, Department of Renal Medicine, Nottingham University Hospital; Dr J. Collison, Consultant Paediatrician, Northampton General Hospital; Dr S. Vijayan, Consultant Paediatrician, Heart of England Foundation Trust and Dr E. Findlay, Consultant Paediatrician, Leeds General Hospital.

Conflict of interest statement
We declare that the results presented in this paper have not been published previously in whole or part, except in abstract format. We have no conflicts of interest.

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