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Original Investigation

Kidney Disease in Adenine Phosphoribosyltransferase Deficiency

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Background: Adenine phosphoribosyltransferase (APRT) deficiency is a purine metabolism disorder causing kidney stones and chronic kidney disease (CKD). The course of nephrolithiasis and CKD has not been well characterized. The objective of this study was to examine long-term kidney outcomes in patients with APRT deficiency.

Study Design: An observational cohort study.

Setting & Participants: All patients enrolled in the APRT Deficiency Registry of the Rare Kidney Stone Consortium.

Outcomes: Kidney stones, acute kidney injury (AKI), stage of CKD, end-stage renal disease, estimated glomerular filtration rate (eGFR), and changes in eGFR.

Measurements: Serum creatinine and eGFR calculated using creatinine-based equations.

Results: Of 53 patients, 30 (57%) were females and median age at diagnosis was 37.0 (range, 0.6-67.9) years. Median duration of follow-up was 10.3 (range, 0.0-31.5) years. At diagnosis, kidney stones had developed in 29 (55%) patients and 20 (38%) had CKD stages 3 to 5, including 11 (21%) patients with stage 5. At latest follow-up, 33 (62%) patients had experienced kidney stones; 18 (34%), AKI; and 22 (42%), CKD stages 3 to 5. Of 14 (26%) patients with stage 5 CKD, 12 had initiated renal replacement therapy. Kidney stones recurred in 18 of 33 (55%) patients. The median eGFR slope was −0.38 (range, −21.99 to 1.42) mL/min/1.73 m^2 per year in patients receiving treatment with an xanthine dehydrogenase inhibitor and −5.74 (range, −75.8 to −0.10) mL/min/1.73 m^2 per year in those not treated prior to the development of stage 5 CKD ($P = 0.001$).

Limitations: Use of observational registry data.

Conclusions: Progressive CKD and AKI episodes are major features of APRT deficiency, whereas nephrolithiasis is the most common presentation. Advanced CKD without a history of kidney stones is more prevalent than previously reported. Our data suggest that timely therapy may retard CKD progression.
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INDEX WORDS: End-stage renal disease; chronic kidney disease (CKD); adenine phosphoribosyltransferase (APRT) deficiency; purine metabolism disorder; nephrolithiasis; kidney stone; crystal nephropathy; estimated glomerular filtration rate (eGFR); renal function; acute kidney injury (AKI); disease progression; kidney failure; renal replacement therapy (RRT).

Adenine phosphoribosyltransferase (APRT) deficiency is an uncommon autosomal recessive disorder of purine metabolism that leads to kidney stones and chronic kidney disease (CKD).[1,2] The absence of APRT activity prevents the recycling of adenine, which instead is catabolized by xanthine dehydrogenase (XDH) to 2,8-dihydroxyadenine (2,8-DHA), a poorly soluble substance excreted by the kidney resulting in heavy crystalluria (Fig 1). More than 40 pathogenic mutations in the coding region of *APRT* have been identified in more than 400 affected people from more than 25 countries,[3,4] most of whom are from France, Iceland, and Japan, whereas fewer than 15 patients originate in the United States.[2] All known pathogenic mutations abolish enzyme function.[1,5]

The phenotype is characterized by radiolucent kidney stones, the most commonly reported clinical manifestation of APRT deficiency, followed by progressive CKD secondary to crystal nephropathy. Kidney failure requiring renal replacement therapy (RRT) is the presenting feature in ∼15% of adult

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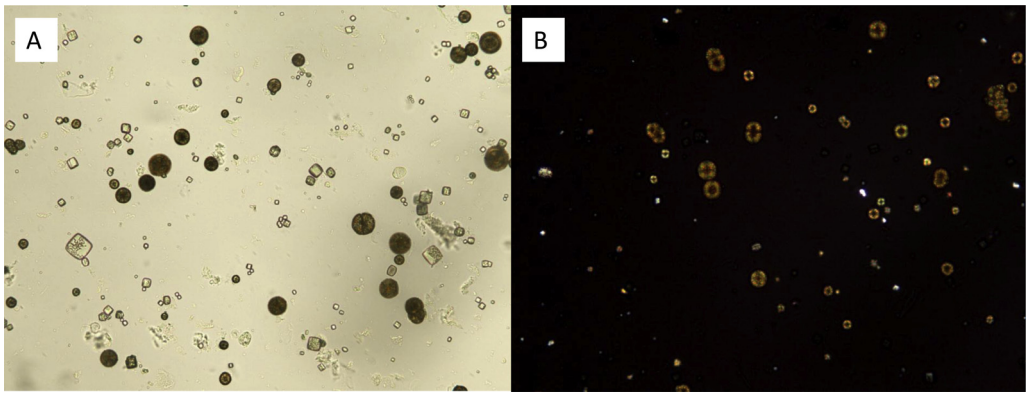

Figure 1. Urinary 2,8-dihydroxyadenine crystals. (A) The characteristic medium-sized crystals are brown with a dark outline and central spicules. (B) The same field viewed with polarized light microscopy shows that the small- and medium-sized crystals appear yellow and produce a central Maltese cross pattern (A, B: original magnification, ×400).

cases.[1,5] In a number of instances, APRT deficiency has first been recognized after kidney transplantation, when transplant dysfunction occurs.[6,7] Other reported clinical manifestations include hematuria and lower urinary tract symptoms. A significant number of patients are asymptomatic at diagnosis.[1,2,8] Treatment with the XDH inhibitor allopurinol has been shown to effectively prevent the progression of kidney disease, and the recently introduced nonpurine XDH inhibitor, febuxostat, has provided an alternative therapeutic option.

Limited data exist on kidney stone recurrence, and the course of kidney function over time has not been well characterized in patients with APRT deficiency. In order to closely examine long-term kidney outcomes, we analyzed data from all persons currently enrolled in the APRT Deficiency Registry of the Rare Kidney Stone Consortium.

METHODS

Study Design

This was an observational cohort study using data from the APRT Deficiency Registry of the Rare Kidney Stone Consortium (www.rarekidneystones.org/). The study was approved by the National Bioethics Committee of Iceland (NBC 09-072) and the Icelandic Data Protection Authority, and informed consent was obtained from all living participants. The clinical and research activities reported are consistent with the Principles of the Declaration of Helsinki. Data from all 53 patients (from Iceland, 33; United States, 13; Austria, 2; Italy, 2; United Kingdom, 1; India, 1; and from Norway of Turkish descent, 1) who enrolled in the registry before November 11, 2014, were included. Limited data for 23 of the 33 Icelandic patients have previously been reported by our group[1] and 5 of the non-Icelandic cases were included in earlier publications.[7,9,10]

Clinical Data

Registry data included age at diagnosis; kidney manifestations, including kidney stones, acute kidney injury (AKI), and stage of CKD; lower urinary tract symptoms; results of urologic imaging studies, kidney stone analysis, and kidney biopsies; surgical treatment of kidney stones; XDH inhibitor treatment; RRT; and cause of death. For calculation of estimated glomerular filtration rate (eGFR) in children, height measurements were obtained from medical records or extrapolated from data points on the growth chart when recent measurements were not available. Laboratory studies included serum creatinine (Scr) measurements; results of urine microscopy, including assessment of 2,8-DHA crystals; *APRT* genotype; and APRT activity.

Definitions

Symptomatic kidney stone events were defined as either patient-reported stone passage or abdominal pain associated with hematuria and/or a stone confirmed by an imaging study. Urinary tract stones identified by imaging only were considered asymptomatic. Stone recurrence was defined as detection of a stone in patients previously shown to be stone free by imaging study. eGFR was calculated from Scr, using the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation in adults[11] and the modified Schwartz equation[12] in children. Nonstandardized Scr values were reduced by 5% before eGFR was calculated, as previously described.[13] All patients were considered to have CKD based on presumed structural damage associated with renal 2,8-DHA crystal deposition. The KDIGO (Kidney Disease: Improving Global Outcomes) classification system was used to stage CKD.[14] Available Scr values were used to identify episodes of AKI, defined according to KDIGO criteria as an increase in Scr level $\geq$ 26.5 μmol/L ($\geq$ 0.3 mg/dL) within 48 hours or 1.5 or more times baseline within 7 days.[15]

Statistical Analysis

Statistical analyses were performed using SPSS (IBM SPSS Statistics, version 21.0; 2012). Data are presented as number, percentage, and median and range. Chi-square analysis was used to compare the prevalence of CKD in Icelandic patients and those from other countries. eGFR slopes and CKD staging were based on annual eGFR values derived from the lowest available Scr measurement in each calendar year, excluding all Scr values obtained during episodes of AKI; patients receiving RRT were assigned an eGFR of 10 mL/min/1.73 m^2. Comparison of eGFR slopes of patients receiving XDH inhibitor treatment and those who were untreated prior to the development of end-stage kidney failure were compared using Mann-Whitney *U* test. Wilcoxon signed rank test was used to compare eGFR slopes of patients before and after the initiation of pharmacotherapy. $P < 0.05$ was considered statistically significant.