Obstructive uropathy and severe acute kidney injury from renal calculi due to adenine phosphoribosyltransferase deficiency

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Background: **Adenine phosphoribosyltransferase (APRT) deficiency is an uncommon genetic cause of chronic kidney disease due to crystalline nephropathy.**

Methods: **A case of a Chinese boy with APRT deficiency presenting with severe acute kidney injury secondary to obstructive uropathy from multiple renal calculi was reviewed.**

Results: **The patient underwent staged removal of the calculi. Infrared spectrometry of the renal calculi showed 2,8-dihydroxyadenine. APRT deficiency was confirmed with abolished APRT enzyme activity in red blood cells. He was started on allopurinol and low purine diet with complete resolution of the residual calculi.**

Conclusion: **APRT deficiency should be considered in patients with multiple radiolucent renal calculi.**

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Key words: **2,8-dihydroxyadenine; acute renal failure; adenine phosphoribosyltransferase deficiency; urolithiasis**

Introduction

Adenine phosphoribosyltransferase (APRT) deficiency is a rare autosomal recessive inborn error of adenine metabolism. The human *APRT* gene is located on chromosome 16. APRT is a purine salvage enzyme that catalyzes the formation of 5'-adenine monophosphate from adenine and 5-phosphoribosyl-1-pyrophosphate. Without APRT, adenine is metabolized by xanthine dehydrogenase to 2,8-dihydroxyadenine (DHA), a highly insoluble compound that crystallizes in the urine, leading to crystalline nephropathy and urolithiasis. We report the first known local case of a child with APRT deficiency who presented with acute renal failure due to obstructive uropathy.

Case report

A 17-month-old Chinese boy presented to the Children's Emergency with vomiting, poor feeding and lethargy of one week duration. He had normal urine output and no history of reddish brown diaper staining or urinary tract infection. He has severe hemophilia A and glucose-6-phosphate dehydrogenase (G6PD) deficiency. His parents are non-consanguineous and there is no known family history of renal calculi.

On examination, he was afebrile, tachycardic (heart rate: 153 beats/minute) and hypertensive (blood pressure: 134/66 mmHg). His biochemistry results showed severe acute kidney injury (serum urea: 55.9 mmol/L; creatinine: 429 μmol/L) with associated hyperkalemia (potassium: 9 mmol/L), hyperphosphatemia (phosphate: 3.7 mmol/L) and metabolic acidosis (bicarbonate: 11 mmol/L). Renal ultrasound revealed bilateral severe hydronephrosis (right and left renal pelvis measuring 1.5 cm and 2.1 cm respectively), hydroureter with multiple renal calculi (measuring: 0.8-1.5 cm) in both kidneys, left pelviureteric junction, right distal ureter and the urinary bladder. These calculi were radiolucent on X-ray.

He underwent continuous veno-venous hemodiafiltration for five days. Good urine output with no urinary discoloration was observed. Urinalysis revealed hematuria with no crystals. Urinary excretion of calcium (calcium/creatinine ratio: 0.3, normal 1.5 for age), uric acid (urine uric acid/creatinine ratio: 0.46, normal 1.3 for age), oxalate (0.25 mmol/1.73 m^2 per

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day, normal <0.5 mmol/1.73 m^2 per day) along with plasma and urine amino acids profile were all normal.

The patient underwent stage surgical removal of the multiple renal calculi. Factor VIII was administered for all the procedures performed. The calculi recovered were bright brown, soft and friable (Fig. 1). Brick red encrustation was also seen on the DJ stent upon removal (Fig. 2). Initial biochemical analysis of the stone showed uric acid. 2,8-DHA was detected via infrared spectrometry stone analysis performed in an overseas center. APRT deficiency was confirmed with red blood cell enzyme assay (0.03 nmol/min/mg hemoglobin, normal 0.15-2.0 nmol/min/mg hemoglobin, residual enzyme activity: 3%). Measurement of 24-hour urine adenine level was not available in the local and regional laboratories.

The patient was subsequently started on allopurinol (5 mg/kg per dose once daily) and low purine diet. 2,8-DHA crystals were not detected on serial urinalysis. At 21 months following the diagnosis, his renal function remained stable (estimated glomerular filtration rate by Modified Schwartz equation was 68 mL/min per 1.73 m^2) with no hypertension or proteinuria and complete resolution of residual stone with no recurrence. Dietary purine restriction had been gradually liberalized. Both his elder sisters were asymptomatic and had normal renal ultrasound findings. The family declined further genetic testing.

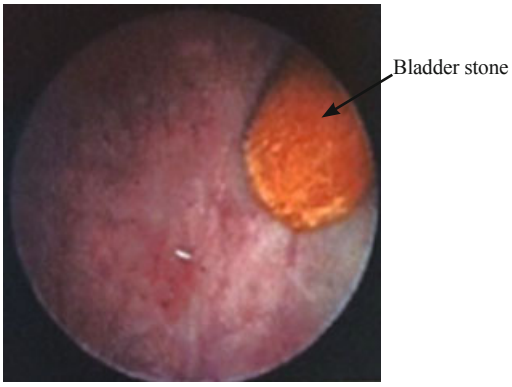

Fig. 1. Bright brown, soft and friable bladder calculi demonstrated on cystoscopy.

Fig. 2. Brick red encrustation along Double J stent.

Discussion

This case illustrates a young child with multiple renal calculi and chronic kidney disease from APRT deficiency who presented with severe acute renal injury from obstructive uropathy. Prompt diagnosis and treatment with allopurinol is essential to prevent crystalline nephropathy which can result in chronic kidney disease.

APRT was first described by Cartier el al[1] in 1974 in a child who presented with urolithiasis due to complete APRT deficiency. Most reported cases are from Japan, France and Iceland.[2-4] None of the reported cases has co-existing hereditary conditions. Our patient also has hemophilia A and G6PD deficiency which are X-linked recessive conditions. The scattered location of the genes involved does not suggest contiguous gene syndrome.

The estimated frequency of heterozygosity was 0.4%-1.1% among Caucasians and higher than 1.2% among Japanese, suggesting worldwide homozygosity of 1:27 000-100 000.[5] The small number of reported cases suggests either under-reporting or under-diagnosis from the following reasons. First, lack of awareness among treating physicians and laboratory technicians due to the rare occurrence of the disease. Second, not all centers have the facility to perform stone analysis via spectrometry. Our case has proven that biochemical stone analysis cannot differentiate uric acid from 2,8-DHA as described in the literature. Last, up to 20% of homozygous patients may remain asymptomatic.[4,6]

The most common clinical presentation of APRT deficiency is radiolucent renal calculi.[3,4,7] Other presentations include acute kidney injury due to urinary tract obstruction from calculi, recurrent urinary tract infections, hematuria and reddish brown diaper stain.[3,4,7-9] Up to 10% of patients had end stage renal failure before diagnosis was made.[2-4,10] Some patients remain undiagnosed and suffered from graft dysfunction soon after kidney transplantation due to crystalline nephropathy.[3,10-12]

Typical histopathological findings in patients with APRT deficiency include intratubular, intracellular and interstitial deposition of DHA crystal with inflammatory changes, which leads to eventual interstitial fibrosis and tubular atrophy.[4,5,9-12] The observed good urine output in this patient despite significant acute kidney injury and urinary obstruction may have been a reflection of

underlying tubulointerstitial injury induced by 2,8-DHA crystal nephropathy causing polyuria.

Treatment of APRT deficiency includes dietary purine restriction and high fluid intake. Allopurinol can prevent further 2,8-DHA excretion and stone formation. Urinary alkalization is not useful as 2,8-DHA is highly insoluble in a wide-range of urinary pH.

In conclusion, early diagnosis with prompt treatment is crucial for patients with APRT deficiency to prevent crystalline nephropathy and renal impairment. APRT deficiency should be considered in pediatric patients who present with multiple radiolucent renal calculi in addition to the conventional investigative approach for renal calculi.

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