Abstract

Adenine phosphoribosyltransferase deficiency is a rare cause of renal stones that, if unrecognized, can lead to renal failure due to deposition of Dihydroxyadenine crystals in the renal tubules. The stones share radiolucency and chemical reactivity with uric acid and xanthine stones and it is difficult to differentiate them on the basis of clinical presentation, radiologic findings and chemical reactions. While dihydroxyadenine urolithiasis is relatively rare worldwide, up to our knowledge, no previous reports from Egypt addressed this issue in children. We report a 4 years old boy with bilateral multiple radiolucent renal stones and recurrent urinary tract infection.

Keywords: Renal stones; Urolithiasis; Adenine phosphoribosyltransferase; Dihydroxyadenine


Introduction

Adenine phosphoribosyltransferase (APRT) deficiency is a rare under-recognized disorder of adenine metabolism. It has a familial tendency and is inherited as autosomal recessive. APRT deficiency eventually leads to increased production of 2,8-dihydroxyadenine (DHA) which has a low solubility at normal range of urine pH resulting in the formation of DHA crystals and recurrent kidney stones as the main presenting feature [1]. Deposition of Dihydroxyadenine crystals in the renal tubules can lead to permanent renal damage with significant morbidity.

Case Report

A four years old boy, born of a consanguineous marriage, presented with a history of discomfort and painful urination with passage of small gravels per urethra for the past 24 hours. He was apparently healthy and had no history of fever, no gross hematuria. There was a past history of faint reddish-brown material in his diapers in the first few months of life. There was a history of two previous urinary tract infections (UTI). The first UTI was during infancy, and the more recent one was 2 months earlier, for which urine culture revealed E coli as the causative organism, and was successfully treated with Amoxicillin-calvulanate (50 mg/kg/day for 10 days) and improved. The parents reported that this child had low thirst threshold and more ingestion of water compared to his siblings. Family history was positive for renal stones in a paternal grandfather. Physical examination revealed normal vital signs for age, apart from tachycardia, mild pallor and mild facial puffiness. Systemic examination showed only mild distension of the abdomen which was mostly gaseous.

Investigations revealed microcytic (MCV 68 fl) hypochromic (21 Pg) anemia (Hb 10.2 g/dL) with high RDW-CV (19.3%), normal kidney function (blood urea 2.8 mmol/L, serum creatinine 27 micromol/L), normal serum sodium (136 mmol/L), potassium (4.2 mmol/L), chloride (99 mmol/L), magnesium (0.8 mmol/L), calcium (2.4 mmol/L), phosphorus (1.6 mmol/L), uric acid (170 mc mol/L) and parathyroid hormone (6.37 pg/mL). Initial urinalysis showed hematuria and moderate uric acid crystalluria (2+). During crystalluria, serum uric acid levels and urinary hyperxaluria panel were normal (glyoxylate 1.8 mg/g creatinine, glycollate 48 mg/g creatinine, glycerate 5 mg/g creatinine, oxalate 87 mg/g creatinine). A plain X-ray of the kidney and urinary tract did not show any radio-opacity and uric acid urolithiasis was the provisional diagnosis.

Abdominal ultrasonography revealed one stone 0.5 mm in diameter in the right kidney with normal renal sinus and multiple stones in the left kidney in the upper, middle and lower calyces, with a total stone burden of 32 mm (Stone upper calyx 10 mm, middle calyx 7 mm and 3 lower calyceal stones, 5 mm each) and hydronephrotic changes (Figure 1). Both ureters showed no distal dilatations or stones. The child was maintained on potassium citrate oral dissolution therapy for uric acid stones with target urine pH between 6.2-6.8.

As he had his first UTI before the age of one year, VCUG was done and showed no VUR. Technetium-99m DMSA showed decreased uptake at the lower pole of the left kidney and MAG3 renogram to assess the split renal function showed that the function of the right kidney is better than the left kidney (with split functions of 56% and 44%, and T1/2 of 5 and 23 minutes, respectively) which suggested a pelviureteric junction (PUJ) obstruction.

We did retrograde ureteropyelogram which showed a normal lower and middle ureter, dilated upper ureter with multiple kinks, normal PUJ with impacted stone (mostly migrated from lower calyx) which resembled PUJ obstruction during the renogram. We did RIRS (retrograde intra-renal surgery) for the PUJ stone using the flexible ureteroscope with laser disintegration and forceps extraction of fragments of the stone for analysis. We failed to reach the other calyceal stones so we decided to insert a double J-shaped (DJ) stent. The fragments of the stone were homogenously faint brown color, friable, and the surface is irregular. A piece of the stone was sent for Infrared Spectrophotometry morphology analysis which surprisingly revealed that the stone is formed exclusively of 2,8-dihydroxyadenine.
Discussion


The early clinical presentation in childhood and the relatively favorable outcome in our case report are similar to other studies in children who reported maintenance of the normal renal function and cessation of urinary excretion of 2,8-dihydroxyadenine during the follow up period [3,4]. The same findings were also noted in a report describing 28 years old female from Japan with APRT deficiency [5]. However the follow up period in these studies (including our report) and in most of the sporadically reported cases in childhood was relatively short. A longer follow up period is needed before we draw the conclusion that early identification of APRT deficiency preserved the renal function in our case. In contrast, studies in adults (where many cases were in the fourth or fifth decades of life) the main presenting feature was crystalline nephropathy and ESRD which necessitated chronic replacement therapy and eventually renal transplantation [6,7]. These reports imply that APRT deficiency is an under-recognized cause of kidney stones and chronic kidney disease that eventually progresses to ESRD in a significant proportion of untreated patients. Early recognition of the disease and prompt institution of effective therapy effectively prevents the development of the grave consequences.

Although the worldwide epidemiology of APRT deficiency is largely unknown, the prevalence is higher in Japan, Iceland and France, due to the higher frequency of certain mutations in these countries [8]. Early recognition of APRT deficiency can be challenging and only few cases have been reported from other part of the world so far. The noted underdiagnosis can be due to the wide spectrum of age of onset from childhood to adulthood, rarity of the disorder and sharing common symptoms with other disorders [9,10]. Up to our knowledge, this is the first case to be reported in a child from Egypt. Causes of under reporting can be due to the lack of awareness of this disorder, inadequate evaluation of patients with kidney stones, where DHA crystals in urine analysis are confused with urate or oxalate, and the wrong diagnosis of radiolucent DHA stones as uric acid stones [11]. We cannot ignore the fact that our provisional diagnosis for this case was uric acid stones and the child was given potassium citrate as a sole treatment and allopurinol was added only after the results of the spectrometric analysis of the stone revealed that it is formed of DHA.

Despite the similar clinical manifestations, two types of APRT deficiency have been described based on the level of residual enzyme activity in vitro studies of erythrocytes. Type I deficiency is characterized by complete enzyme deficiency in intact cells and in cell

Non contrast CT abdomen showed the aforementioned stones with density ranging from 250-450 Hounsfield units. ESWL was the suggested management of the existing stones. The patient was treated with an electromagnetic Lithotripter S under general anesthesia. A single dose of first-generation cephalosporin (50 mg/kg) was given intravenously before induction. SWL protocol was of a total count of 2000 per session at 12 to 14 kV power and a frequency of 60 to 70 per minute. Renal ultrasound (RUS) was used for monitoring during ESWL. The patient underwent staged sessions of SWL, 3 weeks apart (first session targeted the upper and middle calyceal stones, lastly the lower calyceal stones) under ultrasound guidance with 2000 shocks until complete disintegration. For the 2 stones in the lower calyx of the left kidney, only one stone was disintegrated and fragmented of the stone were expelled in urine. The child received 15 mg/kg dose of oral paracetamol every 8 hours for 3 days and was instructed to maintain a high oral fluid intake.

The child was maintained on allopurinol (10 mg/kg/day), potassium citrate, and antibiotic prophylactic therapy for UTI (Nitrofurantoin 2 mg/kg/d). He was advised to increase fluid intake and avoid purine rich food; a list of purine-rich food was given to parents. The DJ stent was removed a month later. On the regular follow-up, Blood urea and serum creatinine are within normal range, no formation of new stones (apart from the 0.5 mm stone in lower calyx of left kidney), and no more passage of gravels per urethra. Surgical intervention (removal) to be considered whenever the stone becomes symptomatic (0.5 mm stone in the lower calyx is less likely to be spontaneously expelled, especially after more than 2 months of follow up).
lysates, whereas type II deficiency is characterized by complete enzyme deficiency in intact cells, but only a partial deficiency in cell lysates. In both types, however, APRT activity is not functional in vivo [12]. APRT deficiency can be efficiently treated with allopurinol 10 mg/kg/day in two divided doses to block xanthine dehydrogenase enzyme and prevent DHA crystalluria and renal damage. Oral dissolution therapy with Potassium citrate is of little help to patients with DHA stones as urinary PH of more than 9 is needed to help dissolution of the existing stones, which is clinically not feasible. Early recognition of APRT deficiency cases is especially important to prevent the progression of these children to ESRD.

References