Clinical Case Reports

Nephrocalcinosis: An interesting case

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ABSTRACT

We report primary hyperoxaluria (PH) type 1 in a young female who presented with a history of right nephrectomy for recurrent renal calculi and pyelonephritis. Genetic study showed it to be a variant of AGXT gene mutation classical of PH type 1.

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INTRODUCTION

With a strong genetic component behind the formation and deposition of calcium stones, primary hyperoxaluria (PH) is a rare autosomal recessive disorder, caused by hepatic peroxisomal enzyme deficiencies. This results in a disorder of oxalate metabolism, leading to increased production and excretion of urinary oxalate complex with calcium, followed by systemic deposition in advanced stages. We report a patient with primary hyperoxaluria who presented with renal calculi, was misdiagnosed as pyonephrosis and finally diagnosed on the basis of a genetic study.

THE CASE

A 30-year-old female was admitted with complaints of nausea, vomiting and abdominal pain for 4 days. Her problems started almost 8 years back with abdominal pain and vomiting for which she was admitted to a private hospital, diagnosed to have right nephrolithiasis with pyelonephritis. She underwent a right nephrectomy for suspected pyonephrosis, for which records were not available. Six months later, she developed similar complaints for which she was admitted to a private hospital, diagnosed as left upper ureteric calculi with hydronephrosis. A double-J stent was placed, stones retrieved and the stent removed after 4 weeks.

After 3 months, she developed nausea and vomiting which was insidious in onset, associated with diffuse, non-colicky abdominal pain. History of loss of weight, loss of appetite and easy fatiguability were present. The patient had no other urinary or systemic symptoms and no history of hypertension, diabetes or other comorbid conditions. The patient had lost all records of her previous treatment. She was born as a third child to non-consanguineous parents. On examination, she was comfortable, thin built, moderately nourished. She was pale, anicteric, and did not have pedal oedema. Systemic examination revealed no positive findings except for a right subcostal transverse scar and right renal angle tenderness on abdominal examination.

She had a haemoglobin level of 5.7 g/dl, total leucocyte count of 6700/cmm, platelet count of 164 000/cmm, an erythrocyte sedimentation rate of 140 mm, random blood sugar of 117 mg/dl, blood urea of 128 mg/dl and serum creatinine of 11.8 mg/dl. Her liver function tests were within normal limits and her serology for HIV, and hepatitis B and C were negative. Her serum uric acid was 9.8 mg/dl (normal 2.6–6 mg/dl), serum calcium 8.0 mg/dl (normal 8.5–10.1 mg/dl), and serum phosphate 4.5 mg/dl. Her serum sodium, potassium and magnesium were within normal limits. Her urine analysis showed albumin ++, 2–6 pus cells, urine spot protein/creatinine ratio 0.11, pH 5.0 and specific gravity 1.025. An ultrasound of the abdomen and pelvis showed acute-on-chronic left pyelonephritis with multiple intrarenal calculi. A CT scan of the abdomen and pelvis showed that her right kidney was absent (history of nephrectomy), and left kidney had evidence of diffuse hyperdensities along the cortical surface, multiple intrarenal calculi in the upper, mid and lower pole, pelvic calculi and possibility of nephrocalcinosis.

In view of recurrent renal calculi, nephrocalcinosis, with renal failure, the absence of hypercalcaemia and hypomagnesaemia, primary hyperoxaluria was suspected and a diagnostic work-up was done. A left ureteroscopy and double J stenting were done but the stones could not be retrieved for analysis. An ophthalmic evaluation was done to look for oxalate crystal deposition in the fundus. However, both eyes had Kayser–Fleischer (KF) ring and the fundus was normal. She had a left brachiocephalic fistula done. A vein biopsy done during the procedure showed no evidence of calcification or oxalate crystal deposition. Her 24-hour urine oxalate/creatinine ratio was 259.3 mg/g (normal <32 mg/g).

A genetic study showed a homozygous missense mutation in exon 6 of the AGXT gene on chromosome 2 that results in the substitution of leucine for serine at codon 205.

DISCUSSION

Primary hyperoxaluria (PH) is of three types. Type 1 occurs from AGXT gene mutation located in the long arm (q) of chromosome 2, where alanine-glyoxylate aminotransferase, hepatic enzyme is deficient. There are about 170 different mutations of AGXT gene, which result in this enzyme deficiency. Type 2 results from a GRHPR gene mutation located in the short arm (p) of chromosome 9, deficient enzymes being D-glycerate reductase and glyoxylate reductase. In type 3, HOGA1 gene located on the long arm (q) of chromosome 10, is mutated causing liver-specific mitochondrial enzyme 4-hydroxy 2-oxoglutarate aldolase deficiency.[1]

There are varied presentations of PH1, ranging from at birth to the sixth decade. The infantile form has a rapid progression by the age of 3 years, recurrent urolithiasis and progressive renal failure in childhood or adolescence, the late-onset form may have urolithiasis or end-stage renal disease (ESRD) as the first symptom, and rarely the diagnosis is detected following recurrence after kidney transplantation. There is an average 5-year interval between initial symptoms and diagnosis in PH1 at which time 10%–40% of patients have ESRD. Early diagnosis

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is achieved in only 30% of cases. Half the patients reach ESRD between 24 and 33 years.[1] In our patient, the course was recurrent renal calculi probably by adolescence, neglected pyonephrosis at 21 years, then diagnosed as PH1 with nephrocalcinosis and ESRD at 30 years of age.

In PH1, there is increased synthesis and urinary excretion of calcium oxalate, which is insoluble in urine and usually presents with urinary symptoms such as urolithiasis or nephrocalcinosis.[2] Once a critical saturation point of plasma oxalate has been reached (>30–50 µmol/L), and the glomerular filtration rate has fallen below 30–50 ml/minute per 1.73 m^2, oxalate deposition occurs in many organs. The systemic involvement commonly involves the bone, heart—the cardiac vessels and conducting system, central nervous system, joints, skin, soft tissues, retina and other visceral lesions. Several methods are useful in diagnosing PH1. Twenty-four-hour urine collection for oxalate measurement corrected for body surface area can be used. Until genetic analysis allowed for the detection of the AGXT gene, which is mutated in 99% of PH1 patients, liver biopsy to measure alanine–glyoxylate transaminase (AGT) catalytic activity was essential for the diagnosis. Liver biopsy is still used in patients with no identified mutation.[1,3,4] In our patient, the suspicion was because of nephrocalcinosis and 24-hour urine oxalate/creatinine ratio of 259.3 mg/g. However, investigations to confirm organ deposition were negative. The genetic study finally confirmed the diagnosis.

The treatment of PH is to increase the urinary solubility of calcium oxalate and decrease oxalate production. This includes high fluid intake (>2 L/m^2 per day), calcium oxalate crystallization inhibitors such as potassium or sodium citrate and elemental phosphorus. Calcium and oxalate intake should remain normal, but excessive vitamin C and D intake should be avoided. Pyridoxine chelates the precursors of oxalate and is metabolized to pyridoxal phosphate, the main co-factor of AGT and around 30% of patients respond to it. Lithotripsy is advised for urolithiasis and haemodialysis for unresponsive patients and those with glomerular filtration rates between 15 and 40 ml per minute per 1.73 m^2, who will eventually require combined liver–kidney transplantation.[5–7] Liver transplantation provides gene and enzyme replacement.[5,7] Our patient did not improve with stenting because of interstitial deposition of oxalate crystals, hence was planned for combined liver–kidney transplantation and started on haemodialysis. She succumbed to her illness from sepsis and dyselectrolytaemia. The United States Renal Data System reports 80% patient survival at 5 years and renal graft survival of 76% at 8 years after combined liver–kidney transplantation. Since oxalate can remain elevated for several years post-transplantation, high fluid intake and crystallization inhibitors should be continued to avoid recurrent nephrocalcinosis, renal calculi and decreased graft function. Gene therapy may be the future of PH1 treatment.

Conflicts of interest. None declared

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